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OFFICE OF
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AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

Date: April 22, 2010

MEMORANDUM

SUBJECT: **Indaziflam: Human Health Risk Assessment** for Use of Indaziflam on Turf, Golf Courses, Sod Farms, Christmas Tree Farms, Non-Crop Areas and Forestry.

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Petition No.: NA	Registration No.: 432-1501
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The Registration Division (RD) requested that the Health Effects Division (HED) conduct a risk assessment for proposed uses of the new active ingredient indaziflam to estimate the risk to human health that will result from proposed uses in residential and commercial lawns, golf course, sod farms, recreational turf, ornamentals, non-crop areas, Christmas tree farms and forested areas.

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1.0 Executive Summary

Indaziflam ([1,3,5-triazine-2,4-diamine,N-[(1R,2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-(1-fluoroethyl)]) is proposed by Bayer CropScience as a selective, pre-emergent and post-emergent alkylazine herbicide for control of many annual grasses and broadleaf weeds in lawns, golf course, sod farms, recreational turf, ornamentals, non-crop areas, Christmas tree farms and forested areas. It is also proposed for use as a pre-emergent herbicide for weed control in parks, railroads, utility, industrial and municipal sites. Indaziflam is proposed for use by commercial and professional applicators (formulated as a water soluble packet and turf fertilizers) as well as residential homeowners (formulated as Lawn 3 FL granules and liquid). It may be applied through a variety of application methods ranging from aerial to hand held equipment. Proposed uses are anticipated to result in short- and intermediate-term durations of exposure. There are currently no registered food uses associated with indaziflam and this is OPP's first human health risk assessment for this chemical.

The toxicology database is considered adequate for selecting toxicity endpoints for this risk assessment. The scientific quality is relatively high, and the toxicity is well-characterized for all types of effects, including potential developmental, reproductive, immunologic and neurologic toxicity. Although at this time the database is considered complete, the Agency is currently evaluating issues related to volatilization of pesticides including the use of route-to-route extrapolation and assessment of inhalation exposure using oral studies, based on the December, 2009 FIFRA Scientific Advisory Panel (SAP) recommendations. The requirement of a 28- or 90-day inhalation toxicity study will be determined when the Agency has completed its review of the SAP report.

The nervous system is a target for indaziflam in rats and dogs. Degenerative neuropathology of the brain, spinal cord and sciatic nerve was reported in the dog following both subchronic and chronic oral exposure. Neuropathology in the dog was the most sensitive effect and was selected as the endpoint for all exposure scenarios involving repeated exposure. In the rat, histopathology of the brain and pituitary *pars nervosa* was observed following chronic exposure. Clinical signs were observed in both species in several studies, which included rat adult and developmental neurotoxicity studies. Decreased motor activity observed in the rat acute neurotoxicity study was selected as the appropriate endpoint for acute oral toxicity.

Decreased body weight/weight gain and other effects on the kidney, liver, stomach, seminal vesicles and ovaries were also observed in rats and/or mice, but only at doses significantly higher than those selected as risk assessment endpoints. Although thyroid effects were observed in male rats, these effects were considered secondary to liver stimulation and also occurred at significantly higher doses than those selected for risk assessment (15-fold or greater), and therefore were not considered to be of concern for pre- and/or postnatal development. Based on the lack of evidence of carcinogenicity or genotoxicity, HED classified indaziflam as "Not likely to be carcinogenic to humans."

Although no food uses are associated with the current request, a food-use petition has been received by the Agency and HED has evaluated the available data with respect to the FQPA safety factor. HED recommends that the FQPA safety factor be reduced to 1X. The toxicity

database for indaziflam is complete, including the required studies that characterize potential susceptibility of infants and children. There was no evidence of increased quantitative or qualitative pre- and/or postnatal susceptibility; developmental effects in the rat were observed only at high doses in the presence of maternal/parental toxicity. Although indaziflam causes neurotoxicity, the effects are well characterized and served as the basis for endpoint selection. Therefore, the risk assessment is protective of potential neurotoxicity and other effects which occurred at higher doses. Conservative, upper-bound assumptions were used to determine exposure through drinking water and residential sources, such that these exposures have not been underestimated.

HED has retained the traditional uncertainty factors for inter-species extrapolation (10X) and intra-species variability (10X). Therefore, HED's level of concern (LOC) is an MOE of 100 and exposure scenarios resulting in MOEs greater than or equal to 100 are not of concern.

HED has assessed residential application and post-application scenarios and determined that risks for these exposures are below the level of concern. HED has also examined the impact of potential residues in drinking water alone and in combination with the residential exposures and found them to be below the level of concern.

HED has also assessed occupational exposures associated with the proposed uses. All risk estimates are below HED's level of concern.

Indaziflam contains a symmetrical triazine moiety and has been reviewed for possible inclusion in the triazine cumulative assessment group of chemicals which include atrazine, simazine, propazine and metabolites diaminochlorotriazine (DACT), desethyl-s-atrazine (DEA), and deisopropyl-s-atrazine (DIA). Based on a comparative review of its structure and toxicological profile indicating that the toxicological effects of indaziflam do not fit the triazine characteristics, HED did not include indaziflam in the triazine cumulative assessment.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), and the Outdoor Residential Exposure Task Force (ORETF) Database, have been determined to require a review of their ethical conduct, have received that review, and have been determined to be ethically conducted.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered for this human health risk assessment, in accordance with US Executive Order 12898, Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations, http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve

pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by USDA under the CSFII, and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, non-dietary exposures based on home use of pesticide products, associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

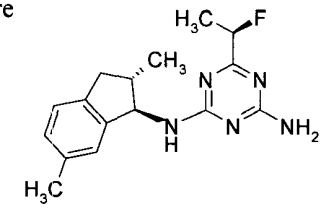
Indaziflam is a selective, pre-emergent and post-emergent alkylazine herbicide proposed for control of many annual grasses and broadleaf weeds in turf (lawns, sod farms, golf courses, recreational fields, etc), ornamentals and trees. It is also proposed for use as a pre-emergent herbicide for weed control in parks, railroads, utility, industrial and municipal sites. Indaziflam is proposed for use by commercial and professional applicators (formulated as a water-soluble packet and turf fertilizers) as well as residential homeowners (formulated as Lawn 3 FL granules and liquid). It may be applied through a variety of application methods including: aerial, ground equipment, right of way handgun, backpack, broadcast and push type spreader, hand held equipment (low pressure, high pressure, pump and trigger sprayer) and hose end sprayer. The herbicide requires rainfall or irrigation within several weeks after application to be activated and effective. The personal protective equipment (PPE) for all proposed commercial labels consists of baseline clothing (i.e., long-sleeved shirt and long pants) and use of chemical resistant gloves. It should be noted that the residential products (i.e., Lawn 3 FL) contain additional active ingredients. This assessment only addresses exposure resulting from the use of indaziflam. Therefore the Registration Division (RD) should ensure that all residential label requests and recommendations intended for Lawn 3 FL products are appropriate for other active ingredients. **Table 2.1** provides a summary of the proposed uses.

Table 2.1: Proposed Commercial and Residential Products and Uses of Indaziflam

Product EPA Reg. No.	Use Site	Application Method	Application Rate	Comments
Commercial Products				
Esplanade 200 SC (Soluble Concentrate) 19% ai	Annual grasses and weeds in non-crop areas (utilities, industrial, municipal and government sites, roadsides) ornamental perennial plantings, around farm buildings, educational facilities, parking lots	Ground Equipment	0.089 lb ai/A	Pre-emergent
		Right of Way	0.089 lb ai/A or 0.0178 lb ai/gal	
		Handgun		
		Low pressure handwand		
		Backpack		
Esplanade F	Forestry	Aerial		Pre-emergent

Table 2.1: Proposed Commercial and Residential Products and Uses of Indaziflam				
Product EPA Reg. No.	**Use Site**	**Application Method**	**Application Rate**	**Comments**
(Flowable Concentrate) 19% ai		Groundboom	0.125 lb ai/A	1 application
		Backpack	0.125 lb ai/A or 0.0248 lb ai/ gal	
BCS-AA107171 20WSP (Water Soluble Packet) 432-RUOO	Annual grasses and weeds in turfgrass, golf courses and sod farms, ornamentals, nurseries, Christmas trees, landscapes, forestry, non-crop areas	Groundboom, Hand held Equipment	0.071 lb ai/A – non-crop areas	Single application in spring, summer and fall; 3 month interval between applications; not to exceed 0.088 lb ai/A per year
BCS-AA10717 0.0142% Plus Turf Fertilizer (granule)	Annual grasses and weeds in turfgrass (golf courses and sod farms; lawns, cemeteries)	Tractor-drawn spreader and push type spreader and belly grinder for use on lawns and parks	0.071 lb ai/A	Not to exceed 0.088 lb ai/A per year
BCS-AA10717 0.0213% Plus Turf Fertilizer (granule)				
BCS-AA10717 0.0284% Plus Turf Fertilizer (granule)				
Residential Products				
Lawn 3FL Concentrate /Ready to spray	Residential lawns, hard scapes and ornamentals	Pump style tank sprayer	0.00063 lb ai/ gallon	
		Hose-end sprayer concentrate; pre-packed hose-end ready to spray; low pressure handwand	0.044 – 0.094 lb ai/A	
Lawn 3FL Granule 0.05% a.i.		Push type spreader and belly grinder	0.044 lb ai/A	Do not repeat applications within 6 months
Lawn 3FL Concentrate Ready to Use		Trigger sprayer	0.00026 lb ai/ gallon	As needed

2.2 Structure and Nomenclature

Table 2.2. Indaziflam Nomenclature	
Compound	Chemical Structure 
Common name	Indaziflam (ISO proposed)
Company experimental names	AE 1170437, BCS-AA10717
IUPAC name	*N*-[(1*R*,2*S*)-2,6-Dimethyl-2,3-dihydro-1*H*-inden-1-yl]-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine
CAS name	1,3,5-Triazine-2,4-diamine, N-[(1R,2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1R)-1-fluoroethyl]-
CAS registry number	950782-86-2, 730979-19-8 (major active isomer), 730979-32-5 (minor active isomer)
End-use product (EP)	Indaziflam 200 SC Herbicide Indaziflam 500 SC Herbicide Esplanade 200 SC Herbicide Esplanade F 200 SC Herbicide Lawn 3FL Herbicide Concentrate/Ready-to-Spray Lawn 3FL Herbicide Granule Lawn 3FL Herbicide Ready-to-Use AA10717 Herbicide Technical AA10717 2% MUP Herbicide AA10717 20WSP Herbicide AA10717 Herbicide 0.0284% Plus Turf Fertilizer AA10717 Herbicide 0.0213% Plus Turf Fertilizer AA10717 Herbicide 0.0142% Plus Turf Fertilizer

Due to the presence of three chiral carbons in the indaziflam structure, there are eight possible isomers for this herbicide. Based on the product chemistry review of the manufacturing use product (MUP) by RD (H. Mukhoty, 12/1/2008, D356393), the registrant is declaring the active ingredient to consist of only isomers "A" (AE 1170437) and "B" (AE 1170438) with concentrations of about 92% and 3%, respectively. Two later RD reviews (S. Malak, 9/22/09, D367608 and 3/18/10, D372513) report additional statements of formula with similar levels of isomer A (92-93%) and isomer B (2.4-2.9%). The chemical name appearing above in Table 2.2 (N-[(1R,2S)...]-6-[(1R) ....diamine) represents that of the A isomer. The name for isomer B is identical to A with the exception of the stereochemistry at the fluorine-bearing carbon (i.e., ...-6-[(1S)...diamine). The remaining six isomers are present at significantly lower levels and are considered to be impurities. The batches used for dosing in the toxicology studies had >90% isomer A, about 1-3% isomer B, and negligible (<1%) levels of the remaining six isomers. These isomer contents are appropriate for the above described composition of indaziflam.

2.3 Physical and Chemical Properties

Table 2.3 Physicochemical Properties of Indaziflam (TGAI Unless Otherwise Noted)

Parameter	Value	Reference
Melting point/range	183 -184 °C indaziflam (pure substance)	Petition Administrative Materials
pH (23 °C)	pH = 6.5 indaziflam (pure substance) pH = 5.1 indaziflam (technical substance)	
Density	1.23 g/cm^3 at 20 °C (both pure and technical substance)	
Water solubility (g/L at 20 °C)	pH 4: 0.0044 pH 9: 0.0028 Distilled water (pH 6.6-6.9): 0.0028	
Solvent solubility (g/L at 20 °C)	Acetone: 55 Acetonitrile: 7.6 Dichloromethane: 150 Dimethyl sulfoxide: >250 Ethanol: 13.0 Ethyl acetate: 47 Heptane: 0.032 Toluene: 4.3	
Vapor pressure	2.5 x 10^{-8} PA at 20 °C or 1.875 x 10^{-10} mm Hg 6.8 x 10^{-8} PA at 25 °C or 5.1 x 10^{-10} mm Hg 6.9 x 10^{-6} PA at 50 °C or 5.2 x 10^{-8} mm Hg	
Henry's law constant	2.69 x 10^{-6} [Pa x m^3/mol] at 20 °C	
Dissociation constant (pK_a)	3.5	
Octanol/water partition coefficient Log (K_{OW})	pH 2: 2.0 pH4, pH7 and pH9: 2.8	
UV/visible absorption spectrum methanol (nm)	λ_{max1} = 213 nm / A = 1.428 λ_{max2} = 268 nm / A = 0.197 λ_{max3} = 291 nm / A = 0.019	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

Studies considered for this assessment included acute lethality (oral, dermal and inhalation routes); primary eye and dermal irritation, dermal sensitization, subchronic oral toxicity (rat, mouse and dog), rat 28-day dermal toxicity, rat acute and subchronic neurotoxicity, dog chronic toxicity, rat chronic toxicity/carcinogenicity, mouse carcinogenicity, developmental toxicity (rat and rabbit), rat two-generation reproductive toxicity (with an additional special non-guideline study evaluating sexual maturation in rats exposed during early development to the triazine-ring metabolite BCS-AA10365, or FDAT), rat developmental neurotoxicity, rat immunotoxicity, genotoxicity, rat general metabolism (Tier 1 and Tier 2), *in vivo* rat dermal absorption and *in vitro* human and rat dermal absorption.

The database is considered complete with the possible exception of a 28 or 90-day inhalation toxicity study in the rat. The Agency is in the process of evaluating expert advice and input on issues related to volatilization of pesticides and route-to-route extrapolation using oral studies for inhalation exposure assessment from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December, 2009 (final report of March 2, 2010; http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html) and determining the appropriate toxicity data needed to assess inhalation exposure. The requirement of an inhalation toxicity study will be determined once scientific guidance and policies on inhalation toxicity have been established.

3.1.1.1 Mode of action, metabolism, toxicokinetic data

Indaziflam is a broad-spectrum, pre- and/or post-emergent herbicide of the fluoroalkyltriazine class. It affects germination of seeds of grasses and broadleaf weeds by inhibiting cell wall biosynthesis and affecting meristematic stem growth. The exact mode of toxicity in mammals is unknown. Metabolism in the rat is discussed below in Section 3.2.

3.1.2 Toxicological Effects

The nervous system is a target for toxicity in rats and dogs. In repeated-dose studies, the dog was the more sensitive species, showing the lowest NOAELs among all available studies, based on neuropathology (degenerative nerve fibers in the brain, spinal cord and sciatic nerve). In the rat, focal/multifocal vacuolation of the median eminence of the brain and the pituitary *pars nervosa* was observed at higher doses. Clinical signs of neurotoxicity were observed in both species in several studies, which included rat adult and developmental neurotoxicity studies, including the rat acute neurotoxicity study. Ophthalmologic effects were also seen in the rat. In the developmental neurotoxicity study, decreased motor activity was observed in 21-day old male pups but was not observed in females at later times. Additional details on neurotoxic effects are found in Section 3.3.2.

In the rat and mouse, effects on the kidney were observed following chronic exposure. Female rats had an increased incidence of dark kidney and basophilic renal tubules. Males in the reproductive toxicity study showed increased kidney weights and incidence of hyaline degeneration and tubular regeneration. In the mouse, males showed decreased kidney weights and increased incidences of collecting duct and pelvic epithelial hyperplasia, papillary necrosis and intratubular yellow-brown material.

Liver cell hypertrophy was observed in the rat following chronic exposure but was considered an adaptive response. In males, white foci were also observed. In females, livers were enlarged and showed an increased incidence of macrovacuolation and multinucleated hepatocytes with anisokaryosis.

The thyroid was affected by treatment only in male rats. Increased follicular cell hypertrophy and colloid alteration were observed. Statistically significant increases in TSH were observed at Week 3, but not at Week 13. There were no significant changes in levels of T3 or T4. Although treatment-related, the thyroid changes were not considered of concern for development because

they appeared to be secondary to liver effects (and induction of liver metabolic enzymes), they were seen at high doses relative to the endpoints selected for risk assessment, and other thyroid hormone levels (T3, T4) did not show changes.

Additional effects observed following chronic exposure included atrophied or small seminal vesicles in male rats and glandular erosion/necrosis in the stomach and blood-filled ovarian cysts/follicles in female mice. However, these effects occurred at higher doses than those at which neurotoxicity was observed in the dog. Decreased body weight gain was observed in most studies following exposure to indaziflam. There was no evidence of immunotoxicity in the available studies, which included a guideline immunotoxicity study in the rat. No systemic effects were observed in the rat following a 28-day dermal exposure period.

In the rat developmental toxicity study, decreased fetal weight was observed in the presence of maternal effects that included decreased body weight and clinical signs of toxicity. No developmental effects were observed in rabbits up to maternally toxic dose levels. Decreased pup weight and delays in sexual maturation (preputial separation in males and vaginal patency in females) were observed in the rat two-generation reproductive toxicity study, along with clinical signs of toxicity, at a dose causing parental toxicity that included clinical signs and decreased weight gain. In the developmental neurotoxicity study, transiently decreased motor activity (PND 21 only) in male offspring was observed and was considered a potential neurotoxic effect. It was observed at a dose that also caused clinical signs of neurotoxicity along with decreased body weight in maternal animals.

Indaziflam showed no evidence of carcinogenicity in the two-year dietary rat and mouse bioassays. All genotoxicity studies that were conducted on indaziflam were negative.

3.1.3 Dose-response

For acute dietary exposure, an acute reference dose (aRfD) of 0.50 mg/kg/day was selected for assessment of all populations, based on a NOAEL of 50 mg/kg/day in the rat acute neurotoxicity study with decreased motor and locomotor activities in females observed at 100 mg/kg/day. This endpoint is a single-dose effect and is appropriate for the populations of concern. Although the rat developmental toxicity study had a lower developmental NOAEL (25 mg/kg/day), the acute neurotoxicity NOAEL of 50 mg/kg/day, with a LOAEL of 100 mg/kg/day, is considered protective for all populations including potentially pregnant females because of the large spread in the dose spacing in the rat developmental study (i.e., NOAEL = 25 and the LOAEL = 200 mg/kg/day). Furthermore, our confidence in the use of the neurotoxicity endpoint is supported by the observed mild effects at the rat developmental LOAEL (200 mg/kg/day), which were limited to pup body weight decrements of <10%.

For chronic dietary exposure, a chronic reference dose (cRfD) of 0.02 mg/kg/day was selected for assessment of all populations, based on a NOAEL of 2.0 mg/kg/day with evidence of nervous system microscopic effects observed at the LOAEL of 6 and 7 mg/kg/day in males and females respectively in the dog chronic dietary study. This provided the most sensitive endpoint available for chronic dietary exposure: rat and mouse chronic exposure NOAELs were ≥12 mg/kg/day.

For short- and intermediate-term residential and occupational exposure scenarios involving incidental oral and inhalation exposure, the NOAEL of 7.5 mg/kg/day from the dog oral subchronic toxicity study was selected. The LOAEL of 15 mg/kg/day was based on nervous system microscopic degenerative effects. Developmental toxicity studies in the rat and rabbit were also available for short-term exposure, but had higher NOAELs (25 mg/kg/day) and, therefore were not considered protective of potential neurotoxicity. The rat subchronic neurotoxicity study also had a significantly higher NOAEL (244 mg/kg/day), as did the developmental neurotoxicity study (maternal and developmental 84 mg/kg/day). The chronic dog study was considered for intermediate-term exposure due to greater incidence and severity of lesions at lower doses with continued exposure, but was not selected because, at one year, the neuropathology at the LOAEL was minimal. Furthermore, based on the proposed use patterns, continuous daily exposures occurring for more than 90 days are not expected to occur.

Although a 28-day dermal toxicity study in the rat was available and showed no toxicity up to the limit dose, including neuropathology or clinical signs, it was not selected for dermal risk assessment because the dog showed considerably greater sensitivity for neuropathology than the rat in the oral studies. The NOAEL from the subchronic dog study was therefore selected to be protective of potential neurotoxicity, but is considered a conservative endpoint due to the bolus (gavage) dosing method employed in the dog subchronic study (similarly, in the chronic dog study animals would consume their treated diets in a relatively short time period).

Long-term dermal and inhalation exposure are not expected; therefore, endpoints were not selected.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The metabolism of indaziflam has been evaluated in the rat using indaziflam labeled with ^{14}C at either the indane or the triazine ring. Indaziflam is rapidly and completely absorbed. Radioactivity was detected in the blood within 5 minutes of dosing. Absorption was estimated at 90% or greater of administered dose, based on bile cannulation experiments. Absorption was slightly more rapid in females than males. Radioactivity was rapidly excreted (approximately 90% of dose by 24 hrs postdosing). Excretion was predominantly fecal at the high dose (1:10 urine:feces). However, at the low dose, urinary excretion was also prominent (1:1 to 1:2 urine:feces), indicating absorption from the gastrointestinal tract was overwhelmed at the higher oral doses. Radioactivity was not retained at significant levels in the tissues by 3 days' postdosing (less than 0.2 to 0.3% of dose), with the highest levels found in the gastrointestinal tract, liver, skin and thyroid. Metabolism was extensive with only 2-12% of the dose excreted in feces as unchanged parent, and occurred primarily via oxidative processes. The major metabolite in the rat was the carboxylic acid metabolite of indaziflam, which was largely excreted in the bile but also found in urine. Other compounds that were identified as major metabolites in combined excreta in one or more groups were 3-hydroxyindane acid, 3-hydroxyindane acid epimer, dihydroxy, hydroxy glucuronic acid, 3-ketoindane acid, and hydroxyethyl acid metabolites. The fluoroethyl diaminotriazine (FDAT) metabolite was identified at low levels (1.18 to 1.69% of administered dose) in the triazine-labeled groups. Some metabolite profile differences were observed depending on the site of the radiolabel. For

example, the dihydroxy and hydroxyethyl acid and acid conjugate metabolites were found in the indane-labeled group, but not the triazine-labeled group. In the bile-duct-cannulated group, the 3-ketohydroxymethyl metabolite was identified in feces but was not found in the mass balance groups. Parent compound was found at higher levels in the triazine-labeled mass balance group than the indane-labeled group, but was present at higher levels in the indane-labeled group in the bile-duct-cannulation experiments. Metabolite profiles in males and females were comparable, with some minor qualitative differences, but females excreted significantly less unchanged parent compound.

3.3 FQPA Considerations

An FQPA assessment is not required for the proposed turf uses of indaziflam. However, because there are proposed food uses pending that will be evaluated subsequent to the turf evaluation, an FQPA assessment has been performed.

3.3.1 Adequacy of the Toxicity Database

The database is considered adequate for assessment of potential sensitivity of infants and children to the effects of indaziflam. Acceptable rat and rabbit developmental toxicity, rat two-generation reproductive toxicity, rat developmental neurotoxicity, rat acute and subchronic neurotoxicity screening and immunotoxicity studies have been submitted. Executive summaries for all of these studies are provided as a separate attachment.

3.3.2 Evidence of Neurotoxicity

Neurotoxicity was observed in the dog and the rat. In the dog, axonal nerve fiber degeneration was observed in the brain, spinal cord and sciatic nerve following subchronic and chronic exposure at the LOAELs (15 mg/kg/day in both sexes in the subchronic study and 6 and 7 in males and females, respectively in the chronic study). The study NOAELs were 7.5 mg/kg/day for the subchronic and 2 mg/kg/day for the chronic study. No clinical signs of toxicity were observed at doses up to 11 and 15 mg/kg/day (chronic/subchronic studies). High dosed dogs in the subchronic study (30 mg/kg/day) were prematurely terminated due to excessive clinical signs including ataxia, tremors, decreased pupil response, seizures and other findings.

In the rat, a marginal decrease in motor/locomotor activity was observed in females in the acute neurotoxicity study at 100 mg/kg (NOAEL = 50 mg/kg). Additional findings at higher doses include tremors, increased reactivity, decreased activity, and urine, oral or perianal staining. Males also showed nerve fiber degeneration of the gasserian ganglion, sciatic nerves and tibial nerves. Similar clinical and motor activity changes were observed in the subchronic neurotoxicity study, although no neuropathology was observed. Decreased motor and locomotor activity in females and clinical signs in both sexes (including tremors, repetitive chewing movements and perianal/lacrimal staining) were reported in the subchronic neurotoxicity study at a higher dose (about 580 mg/kg/day with a NOAEL of 244 mg/kg/day) than the acute study, probably as a result of gavage vs. dietary exposure. The clinical signs were consistent with neurotoxicity, but also could have been due to systemic toxicity. In addition, similar clinical findings were seen in P and F1 generation animals in the reproductive toxicity study, at doses

≥318 mg/kg/day. Clinical signs of neurotoxicity following chronic dietary exposure to the rat at dietary concentrations ≥12 mg/kg/day were numerous and included dilated pupil, reduced motor activity, movement and posture abnormalities, soiling and staining, tremors, reduced alertness, labored, rapid or noisy respiration, piloerection and ophthalmological abnormalities, including mydriasis, absent papillary reflex and pale fundus. At terminal sacrifice, focal/multifocal vacuolation of the median eminence in the brain and of the *pars nervosa* was seen in males and females and peripheral or bilateral retinal atrophy in females. Neurotoxicity was not observed in the mouse.

In a developmental neurotoxicity study on indaziflam, pregnant rats were administered indaziflam at dietary concentrations of 0, 150, 1000 or 7000 ppm; equivalent to average daily intakes of 0, 13, 83.8 or 432 mg/kg/day. The high dose, originally at 7000 ppm, was reduced to 4000 ppm on LD 4. Maternal and offspring toxicity were observed only at the high dose of 432 mg/kg/day. Maternal clinical signs (daily observations and/or FOB) include coarse tremor, dilated pupils or dilated pupils that were unresponsive to penlight, nasal staining and repetitive chewing movements. Maternal body weight and weight gain were decreased during gestation and lactation. The number of litters was reduced by 17%. In the offspring, body weights were also decreased in both sexes from PND 1 through lactation; postweaning males also had lower body weights. A statistically significant decrease in motor activity (29%) on PND 21 was observed in males only at higher doses; although no changes were seen at other assessment times or in females, it was considered treatment-related because it was statistically significant and outside the laboratory historical control range.

3.3.3 Developmental Toxicity Studies

Acceptable developmental toxicity studies in the rat and rabbit are available. In the rat, maternal body weight gain and food consumption were decreased at 200 mg/kg/day. Decreased fetal body weight was observed at 200 mg/kg/day. The maternal and developmental NOAEL was 25 mg/kg/day. In the rabbit, decreased maternal body weight gain and food consumption, and macroscopic liver changes in one doe (pallor, white foci) were observed at 60 mg/kg/day, but no developmental effects were observed. The maternal NOAEL was 25 mg/kg/day and the developmental NOAEL was 60 mg/kg/day. The developmental neurotoxicity study is described above in Section 3.3.2.

3.3.4 Reproductive Toxicity Studies

In the reproductive study parental toxicity was observed only at the high dose (≥317 mg/kg/day) and includes coarse tremors in females during premating, gestation and lactation, decreased body weight gain and food consumption in both sexes and kidney effects in males (increased absolute and relative weight and hyaline degeneration/regeneration). Offspring toxicity was also observed only at the high dose. Clinical signs of toxicity in F1 pups included perianal, urine and nasal stains, tremors, increased reactivity and activity, myoclonus, and diarrhea but no signs were seen in F2 pups. F1 pup weights were decreased through the postnatal period for males and females. Reproductive toxicity was observed as delays in achieving sexual maturation at the high dose, as measured by preputial separation (males) and vaginal opening (females), in the F1 and F2 offspring. The NOAEL for parental, offspring and reproductive toxicity was 69.3 mg/kg/day.

3.3.5 Additional Information from Literature Sources

No published studies, relevant to human hazard resulting from use of indaziflam, were identified.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There was no evidence of increased susceptibility (qualitative or quantitative) for pre- and/or postnatal effects in developmental toxicity studies in the rat and rabbit, the rat developmental neurotoxicity study or the rat two-generation reproductive toxicity study. There is no concern and there are no residual uncertainties for qualitative or quantitative pre- and/or postnatal susceptibility to indaziflam. This is based on the completeness of the database, lack of evidence of increased susceptibility, and the selection of endpoints with low NOAELs that are adequately protective of potential developmental effects. Delayed sexual maturation in offspring was observed at the highest dose of the reproductive toxicity study in the presence of maternal toxicity. Effects in offspring in the developmental neurotoxicity study (decreased motor activity in males on PND 21 were well characterized and were only observed at doses that caused maternal neurotoxicity. Although treatment-related thyroid histological changes (following subchronic or chronic exposure) and transiently increased TSH (at Week 3 but not Week 14) were observed in male rats, they are not of concern for developmental effects because they were only observed in the males, were observed at a high dose relative to the selected regulatory endpoints, and appear to be secondary to liver effects.

3.4 FQPA Safety Factor for Infants and Children

HED recommends reduction of the FQPA safety factor to 1X. The toxicity database for indaziflam is complete, including the required studies that characterize potential susceptibility of infants and children. There was no evidence of increased quantitative or qualitative pre- and/or postnatal susceptibility; developmental effects in the rat were observed only at high doses in the presence of maternal/parental toxicity. Although indaziflam causes neurotoxicity, the effects are well characterized and served as the basis for endpoint selection. Therefore, the risk assessment is protective of potential neurotoxicity and other effects which occurred at higher doses. Conservative, upper-bound assumptions were used to determine exposure through drinking water and residential sources, such that these exposures have not been underestimated.

Although the dog is the more sensitive species, the results of the rat developmental neurotoxicity study, which thoroughly examined potential effects to the developing nervous system following pre- and post-natal exposure, showed only marginal effects in offspring (slightly decreased motor activity, absolute brain weight) at relatively high (and maternally toxic) doses and indicates that increased susceptibility does not occur.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – All Populations Including Infants and Children and Females Age 13-49

Study Selected: Acute Neurotoxicity – Rat
MRID Nos: 47443310
Dose and Endpoint for Risk Assessment: NOAEL = 50 mg/kg, based on decreased motor and locomotor activity in females at 100 mg/kg.
Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)

$$\textbf{Acute RfD} = \frac{50\ mg\ /\ kg}{100\ (UF)} = \textbf{0.50 mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factors: The selected NOAEL of 50 mg/kg is from a study of the appropriate route and duration. The decreases in motor and locomotor activity are considered potential single-dose effects because they were observed within the first hours following dosing. The endpoint is protective of the decreases in maternal body weight gains seen within the first three days of exposure in the developmental rat (25/200 mg/kg/day, NOAEL/LOAEL) and rabbit (25/60 mg/kg/day, NOAEL/LOAEL) toxicity studies, but which were considered questionable as an endpoint due to variability in the data. No other acute effects were observed in the database. The endpoint is also protective of potential developmental effects, based on the lack of observed increased pre- and/or postnatal susceptibility and higher LOAELs observed in developmental, reproductive, neurotoxicity, developmental neurotoxicity and immunotoxicity studies. Although the rat developmental toxicity developmental NOAEL was lower (25 mg/kg/day), the neurotoxicity NOAEL of 50 mg/kg is considered protective because the rat developmental LOAEL (7-9% decrease in fetal body weight) was significantly greater (200 mg/kg/day) and the effects were relatively mild at that dose and unlikely to occur after a single dose.

3.5.2 Chronic Reference Dose (cRfD)

Study Selected: Chronic Toxicity (Dietary) – Dog
MRID No: 47743294
Dose and Endpoint for Risk Assessment: NOAEL = 2.0 mg/kg/day, based on nerve fiber degeneration in the brain, spinal cord and sciatic nerve at 6 and 7 mg/kg/day (M and F respectively).
Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)

$$\textbf{Chronic RfD} = \frac{2.0\ mg\ /\ kg\ /\ day}{100\ (UF)} = \textbf{0.02 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors: The NOAEL selected for this risk assessment represents the lowest available NOAEL for effects of indaziflam

following long-term dietary administration. The RfD is protective of potential developmental effects, based on the lack of observed increased pre- and/or postnatal susceptibility and significantly higher NOAELs observed in developmental, reproductive, neurotoxicity, developmental neurotoxicity and immunotoxicity studies.

3.5.3 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Subchronic Toxicity (Gavage) – Dog
MRID No: 47743289
Dose and Endpoint for Risk Assessment: NOAEL = 7.5 mg/kg/day, based on brain, spinal cord and sciatic nerve degenerative lesions at 15 mg/kg/day.
Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from an oral study of appropriate exposure duration (90-days) for short-term (up to 30 days) and intermediate-term (up to 6 months) exposure via the oral route. The selected endpoint is protective of potential postnatal developmental toxicity, based on the lack of observed postnatal susceptibility and significantly higher NOAELs for postnatal toxicity in the developmental neurotoxicity and the two-generation reproductive toxicity studies.

3.5.4 Dermal Absorption

In addition to a 28-day study evaluating dermal toxicity in the rat, an *in vivo* dermal absorption study in the rat and *in vitro* dermal absorption studies in the rat and human were submitted. The data demonstrated an inverse relationship between dosing concentration and percent absorption. Based on *in vivo* dermal absorption observed in the rat and *in vitro* comparative rat:human absorption data, an estimated human dermal absorption factor (DAF) of 7.3% was obtained.

The human DAF was calculated as follows (all absorption values adjusted for recovery): (1) in the rat *in vivo* dermal absorption study, 27.39% of the applied dose was absorbed at 24 hrs postexposure (actual exposure time 8 hrs) using an application of 0.0005 mg/cm^2; (2) *in vitro* exposure of microtomed rat skin under the same exposure and assessment conditions gave a dermal absorption of 22.40%; (3) the ratio of the *in vitro* to the *in vivo* absorption is 0.82 (22.4/27.39) and therefore is close to 1, indicating that the *in vitro* data is predictive of *in vivo* absorption; (4) based on this ratio, a DAF for humans may be calculated using *in vitro* human dermal absorption (5.975%, adjusted for recovery) observed *in vitro* under the same exposure conditions. The DAF for humans is therefore 5.975%/0.82 = 7.3%.

3.5.5 Dermal Exposure (Short-Term, 1-30 days, and Intermediate-Term, 1-6 months)

Study Selected: Subchronic Toxicity-Dog
MRID No: 47743289
Dose and Endpoint for Risk Assessment: NOAEL = 7.5 mg/kg/day, based on degenerative brain, spinal cord and sciatic nerve fiber lesions at 15 mg/kg/day.

Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from a study of appropriate exposure duration (90 days) for short- and intermediate-term exposure. The subchronic oral dog study was selected over other studies because the dog was the most sensitive species for neurotoxicity and had the lowest overall NOAEL. Although a 28-day dermal toxicity study in the rat showed no effects at the limit dose (including neuropathology), it was not selected as an endpoint for this exposure scenario due to the significantly greater sensitivity for neurotoxicity seen in the dog relative to the rat. Neurotoxic effects in the dog were identified at doses that were 10-20 times lower than in the rat. The endpoint is nonetheless considered conservative because the effects in the dog were observed following gavage dosing, in contrast to a relatively slower dermal absorption rate. For route-to-route extrapolation, dermal absorption of 7.3% relative to oral absorption was used, estimated from human and rat *in vitro* and rat *in vivo* dermal absorption.

3.5.6 Dermal Exposure (Long-Term, >1 year)

Long-term dermal exposures are not anticipated from occupational activities.

3.5.7 Inhalation Exposure (Short-Term, 1-30 days and Intermediate-Term, 1-6 months)

Study Selected: Subchronic Toxicity-Dog
MRID No: 47743289
Dose and Endpoint for Risk Assessment: NOAEL = 7.5 mg/kg/day, based on degenerative brain, spinal cord and sciatic nerve fiber lesions at 15 mg/kg/day.
Uncertainty Factor: 100X (10X interspecies extrapolation, 10X intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors: The selected endpoint is the most sensitive NOAEL available from a study of appropriate exposure duration (90-days) for short- and intermediate-term exposure. The subchronic oral dog study was selected over other studies because the dog was the most sensitive species for neurotoxicity and overall lowest NOAEL. For route-to-route extrapolation, inhalation absorption of 100% is assumed relative to oral absorption because there are no data on inhalation absorption and a route-specific inhalation study is not available.

3.5.8 Inhalation Exposure (Long-Term)

Long-term inhalation exposure scenarios are not anticipated for occupational exposures.

3.5.9 Level of Concern for Margin of Exposure

Table 3.5.9. Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1 - 30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100	100	NA
Inhalation	100	100	NA
Residential Exposure			
Dermal	100	100	NA
Inhalation	100	100	NA
Oral	100	100	NA

NA = not applicable

3.5.10 Recommendation for Combining Routes of Exposure for Risk Assessments

When there are potential occupational and residential exposures to the pesticide, the risk assessment must address exposures from three major sources: oral, dermal and inhalation exposures and determine whether the individual exposures can be combined if they have the same toxicological effects. Since the dermal, inhalation and oral endpoints are based on the same effects (neuropathology) these routes of exposure may be combined for purposes of this risk assessment.

3.5.11 Classification of Carcinogenic Potential

There was no evidence of carcinogenicity observed in the two-year dietary rat or mouse carcinogenicity bioassays. Genotoxicity studies (reverse gene mutation in bacteria, forward gene mutation in mammalian cells and *in vitro* and *in vivo* chromosomal aberration assays) were negative. Based on the lack of evidence of carcinogenicity or genotoxicity, HED classified indaziflam as "Not likely to be carcinogenic to humans."

3.5.12 Acute Toxicity

Indaziflam shows low acute toxicity by all routes of exposure (Toxicity Category III, oral and dermal and Category IV, inhalation) and is not an ocular or dermal irritant or a dermal sensitizer.

3.5.13 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments of Indaziflam

Table 3.5.13. Summary of Toxicological Doses and Endpoints for Indaziflam for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children and Females 13-49 years of age)	NOAEL = 50 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X	Acute RfD = 0.5 mg/kg/day aPAD = 0.5 mg/kg/day	Acute oral neurotoxicity in the rat LOAEL = 100 mg/kg/day, based on decreased motor and locomotor activity in females.
Chronic Dietary (All Populations)	NOAEL = 2 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X	Chronic RfD = 0.02 mg/kg/day cPAD = 0.02 mg/kg/day	Chronic oral (dietary) toxicity in the dog LOAEL = 6/7 mg/kg/day M/F, based on nerve fiber degenerative lesions in the brain, spinal cord and sciatic nerve.
Incidental Oral, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic oral (gavage) in the dog LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Dermal, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day DAF = 7.3%	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic oral (gavage) in the dog LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Dermal, Long-Term (>6 months)	Not required for this assessment (exposure is seasonal; long-term occupational exposure scenarios are not anticipated).			
Inhalation, Short-term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day Inhalation absorption assumed to be 100% (default) relative to oral.	UF_A=10X UF_H=10X FQPA SF = 1X	Residential LOC for MOE = 100	Subchronic oral (gavage) in the dog LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Inhalation, Long-term (>6 months)	Not required for this assessment (exposure is seasonal; long-term occupational exposure scenarios are not anticipated).			

Table 3.5.13. Summary of Toxicological Doses and Endpoints for Indaziflam for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable. DAF = dermal absorption factor

Table 3.5.13 Summary of Toxicological Doses and Endpoints for Indaziflam for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal, Short-Term (1 to 30 days) and Intermediate-term (1 to 6 months)	NOAEL = 7.5 mg/kg/day DAF = 7.3%	UF_A=10X UF_H=10X	Occupational LOC for MOE = 100	Subchronic oral (gavage) in the dog LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Dermal, Long-Term (>6 months)	Not required for this assessment (exposure is seasonal; long-term occupational exposure scenarios are not anticipated).			
Inhalation Short-Term (1 to 30 days) and Intermediate-Term (1 to 6 months)	NOAEL= 7.5 mg/kg/day. Inhalation absorption assumed to be 100% (default) relative to oral.	UF_A=10X UF_H=10X	Occupational LOC for MOE = 100	Subchronic oral (gavage) in the dog LOAEL = 15 mg/kg/day, based on axonal degenerative microscopic findings in the brain, spinal cord and sciatic nerve.
Inhalation Long-Term (> 6 months)	Not required for this assessment (exposure is seasonal; long-term occupational exposure scenarios are not anticipated).			
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. DAF = dermal absorption factor.

3.6 Endocrine disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans or wildlife similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identity any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors. Indaziflam is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408 (p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Public Health and Pesticide Epidemiology Data and Incident Reports

There are no public health, pesticide epidemiology or incident data to report at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Degradates of Concern

OPP performed a preliminary review of the available metabolism and environmental fate data for purposes of determining the residues of concern for drinking water by the Residues of Concern Knowledgebase Subcommittee (ROCKS) (G. Kramer, D371659, February 18, 2010). Conclusions regarding residues of concern for metabolites in proposed crops and livestock are not pertinent to this assessment and will be addressed in a future, separate risk assessment for indaziflam.

Several environmental degradates are of concern for drinking water risk assessment. Drinking water residues of concern for this purpose include triazine indanone, indaziflam carboxylic acid, FDAT, dihydroamino triazine, indaziflam hydroxyethyl, and indaziflam olefin. With the exception of FDAT and dihydroamino triazine, all of the metabolites are assumed to have comparable toxicity to the parent due to structural similarity (i.e., both rings intact). FDAT is not expected to be more toxic than the parent indaziflam based on FDAT's non-neurotoxic mode of action (E. Scollon, D371661, April 21, 2010). Therefore, the neurotoxic endpoints selected for this risk assessment will be protective of potential FDAT toxicity. Dihydroamino triazine (ROI1) is assumed to have comparable toxicity to FDAT. A summary of the metabolites and degradates is provided in **Table 5.1**. Structures of these compounds are shown in Appendix C.

Drinking Water	Indaziflam + FDAT + Triazine indanone + Indaziflam carboxylic acid + Indaziflam hydroxyethyl + Indaziflam olefin + Dihydro-amino triazine	Not Applicable

5.1.1 Drinking Water Residue Profile

(Tier 2 Drinking Water Exposure Assessment for the Section 3 New Chemical Registration of Indaziflam; R. Baris, D356141; February 2, 2010)

Based on a review of the available environmental fate data, the ROCKS determined that the four major transformation products that maintain the dual ring structure of indaziflam should be included in the drinking water exposure assessment since they may be of toxicological concern (i.e., they are assumed to be of equal or lower toxicity to the parent in the absence of toxicological data). These transformation products include: triazine indanone, indaziflam-carboxylic acid, indaziflam-olefin, and indaziflam-hydroxyethyl. In order to account for residues of these transformation products, the Environmental Fate and Effects Division (EFED) calculated drinking water concentrations for total indaziflam residues which included indaziflam and similarly structured degradates. EFED also calculated separate concentration estimates for FDAT plus dihydroamino triazine (ROI1; a degradate of FDAT). Drinking water concentrations were based on maximum seasonal application rates for the anticipated future use on citrus (0.134 lb ai/A), which is higher than turf application rates (0.094 lb ai./A) and thus protective of drinking water scenarios and populations. As noted above, HED has included the residue estimates for FDAT and ROI1 directly in the indaziflam assessment due to the available toxicity data indicating the neurotoxic endpoints for indaziflam are protective of toxicity from these degradates. The drinking water concentrations used to estimate exposure via drinking water are included in **Table 5.1.1**.

Table 5.1.1 Summary of Estimated Surface Water and Groundwater Concentrations for Indaziflam

Exposure Duration	Indaziflam		FDAT + ROI1		Combined*	
	Surface, ppb [a]	Ground, ppb [b]	Surface, ppb [a]	Ground, ppb [b]	Surface, ppb	Ground, ppb
Acute	48	1.6	19	1.1	84	3.7
Chronic (non-cancer)	14	1.6	6	1.1	26	3.7

* Residue estimates for FDAT and ROI1 have been converted to indaziflam equivalents (molecular weight ratio = 301÷157 = 1.92) and included directly in the indaziflam concentration estimates.
[a] From the PRZM and EXAMS
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.134 lb ai/A for citrus.

Field and laboratory data indicate that indaziflam and its degradates have a potential to leach to ground water, particularly FDAT. Indaziflam is classified as moderately mobile; however, transformation products of indaziflam are mobile to highly mobile and were detected in field studies at depth. Further, data show that indaziflam is persistent in anaerobic soil and anaerobic aquatic systems. There are no data available on the anaerobic degradation of the transformation products of indaziflam. Key lines of evidence show that residues of indaziflam, and degradate products (e.g., FDAT) are a concern for exposure via ground water. A prospective ground water study could help reduce the uncertainty regarding the exposure via ground water.

5.2 Dietary Exposure and Risk

A screening level drinking water exposure risk assessment was conducted using the Dietary Exposure Evaluation Model Database (DEEM-FCID ^{TM}). While there are currently no food exposures associated with the proposed new use (i.e., turf), discussion of acute and chronic dietary exposure via drinking water is provided for purposes of completing the combined assessment. For acute and chronic drinking water assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). For food-use pesticides, this dose is referred to as the population-adjusted dose (PAD) typically reserved for food uses. As indicated previously, the Agency is currently reviewing new proposed food uses associated with a separate action. For the purposes of facilitating the future indaziflam food uses (under current review), HED has incorporated the use of the PAD in this assessment. The PAD is equivalent to the reference dose (RfD) divided by the FQPA Safety Factor. For acute and chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

Acute and chronic drinking water risk estimates are not of concern for general population or other population subgroups. The subgroup with the highest risk estimate was infants less than one year old with an aPAD of 3% and a cPAD of 9.0%. The aPAD for the general population was <1% and the cPAD was 2.7%. The results of the acute and chronic dietary exposure analysis are reported in **Table 5.2**.

Table 5.2. Result of Chronic Dietary Exposure and Risk Estimates for Indaziflam			
Population Subgroup	**Acute Dietary Exposure (mg/kg/day)** [1]	**% aPAD** [2]	**MOE** [3]
General U.S. Population	0.004388	< 1	11,000
All Infants < 1 yr old	0.016544	3	3,000
Children 1-2 yrs old	0.006885	1	7,200
Children 3-5 yrs old	0.006290	1	7,900
Children 6-12 yrs old	0.004379	< 1	11,000
Youth 13-19 yrs old	0.003560	< 1	14,000
Adults 20-40 yrs old	0.004066	< 1	12,000
Adults 50+ yrs old	0.003671	< 1	13,000
Females 13-49 yrs old	0.004089	< 1	12,000
Population Subgroup	**Chronic Dietary Exposure**	**% cPAD**	**MOE**
General U.S. Population	0.000548	2.7	3700
All Infants < 1 yr old	0.001797	9.0	1100
Children 1-2 yrs old	0.000814	4.1	2500
Children 3-5 yrs old	0.000762	3.8	2600
Children 6-12 yrs old	0.000525	2.6	3800
Youth 13-19 yrs old	0.000396	2.0	5100
Adults 20-40 yrs old	0.000512	2.6	3900
Adults 50+ yrs old	0.000538	2.7	3700
Females 13-49 yrs old	0.000510	2.5	3900

1. Output from dietary exposure (drinking water only) assessment
2. % PAD = Exposure (mg/kg/day)/(aPAD = 0.5 mg/kg/day or cPAD = 0.02 mg/kg/day)
3. Acute Dietary MOE = Acute Dietary NOAEL (50 mg/kg/day)/acute dietary exposure (mg/kg/day))
   Chronic Dietary MOE = Chronic Dietary NOAEL (2 mg/kg/day)/chronic dietary exposure (mg/kg/day)

5.2.1 Cancer Dietary Risk

HED has classified indaziflam as "not likely to be carcinogenic to humans." Based upon this classification, HED has determined there is no cancer risk associated with the proposed uses.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

(Occupational and Residential Exposure Assessment for Use of the New Active Ingredient Indaziflam on Turf, Golf Courses, Sod Farms, Christmas Tree Farms, Non-Crop Areas and Forestry; M. Collantes: April 2010; D372538)

6.1 Residential Handler Exposure

Three indaziflam residential turf products (i.e., Lawn 3 FL Concentrate/Ready-to-Spray, Lawn 3 FL Granule, and Lawn 3 FL Ready-To- Use) are proposed for use by home owners. These products are to be applied using hand held sprayers (pump style tank, hose end, and trigger) or push-type spreaders. No chemical-specific unit exposure data were provided in support of this submission; therefore, the Pesticide Handlers Exposure Database (PHED) Surrogate Exposure Guide and Outdoor Residential Exposure Task Force (OREFT) study (MRID 44972201) unit exposures were used to estimate handler exposure. Exposures are expected to be short- and intermediate-term in duration.

HED's level of concern for risks (i.e., margin of concern (MOE)) for indaziflam is 100 for residential exposure. Handler dermal, inhalation and total (dermal + inhalation) MOEs were

significantly greater than 100 (ranging from 3,000 to 510,000) and therefore not of concern to HED. Handler exposure and risk is summarized in **Table 6.1.2**.

Table 6.1.2: Indaziflam Residential Handler Exposure and Risk										
Turf Exposure Scenarios	**Use Site**	**Dermal Unit Exposure (mg/lb) [a]**	**Inhalation Unit Exposure (mg/lb) [a]**	**Application Rate [b] (lb ai/acre)**	**Area Treated (A/day)**	**Dermal Dose [c] (mg/kg/day)**	**Dermal MOE [d]**	**Inhalation Dose [e] (mg/kg/day)**	**Inhalation MOE [f]**	**Total MOE [g]**
Mixer/Loader/Applicator										
1. Hose-end Sprayer "Mix Your Own" (ORETF – OMA004))	lawns, hardscapes and ornamentals	11	0.017	0.094	0.5	0.000539	14,000	1.14E-5	660,000	14,000
2. Belly Grinder (PHED) 72155-OR		110	0.062	0.044		0.00252	3000	1.95E-5	380,000	3000
					0.023	0.00011	68,000	8.96E-7	8,000,000	67,000
3. Hand-Held Pump Sprayer (ORETF-OMA005) 72155-IO		56	0.0038	0. 00063 lb ai/gal	5 gallons	0.000184	41,000	1.71E-7	44,000,000	40,000
Applicator										
4. Trigger sprayer Ready to Use (ORETF – OMA006) 72155-ON		54	0.0019	0.00026 lb ai/gal	1 gallon	0.000014	510,000	7.0E-9	1,000,000,000	510,000
5. Granular Push Spreader (ORETF – OMA003) 72155-OR	lawns	0.67	0.00088	0.044	0.5	0.0000154	490,000	2.77E-7	27,000,000	480,000
6. Hose End Sprayer Ready to Use (ORETF – OMA004) 72155-IO	lawns, hardscapes and ornamentals	2.6	0.011	0. 094		0.000127	59,000	7.39E-6	1,000,000	56,000

a. Application Rate based on proposed labels
b. Dermal Dose = Unit Exposure (mg/lb) x Application Rate (lb ai/acre or lb ai/gal.) x Area Treated (acre/day or gal./day) x 7.3% dermal absorption factor/BW
c. Dermal MOE = NOAEL (7.5 mg/kg/day)/Dermal Dose (mg/kg/day)
d. Inhalation Dose = Unit Exposure (mg/lb) x Application Rate (lb ai/acre or lb ai/gal.) x Area Treated (acre/day or gal./day)/BW
e. Inhalation MOE = NOAEL (7.5 mg/kg/day)/Inhalation Dose (mg/kg/day)
g. Total MOE = NOAEL (7.5 mg/kg/day)/ (dermal dose + inhalation dose) mg/kg/day

6.2 Residential Postapplication Exposure

Indaziflam residential postapplication scenarios include children (3 to 6 years) playing on treated turf, adults performing yard work on treated turf and adults playing golf on treated turf. As a result, a wide array of individuals of varying ages can potentially be exposed when they do activities in areas that have been treated. Postapplication dermal exposures for adults and children, as well as oral non-dietary ingestion exposures for children (i.e. soil ingestion, and hand-/object-to-mouth) resulting from commercial and residential applications were assessed. Although a chemical specific turf transferable residue (TTR) study was submitted and reviewed by HED (AE 1170437 20WP Determination of transferable Residues from Turf; D. Fischer, June 2008; MRID #47443316), all dermal and oral postapplication exposures were assessed using default assumptions and transfer coefficients from the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments, 2000. Residential postapplication exposures resulting in MOEs greater than or equal to 100 are not of concern.

6.2.1 Inhalation Postapplication Exposure

Based on the Agency's current practices, a quantitative postapplication inhalation exposure assessment was not performed for indaziflam at this time primarily because it has a very low vapor pressure (vapor pressure 5 x 10^{-10} mmHg at 25°C), it is applied at low application rates (maximum rates range from 0.089 - 0.125 lbs ai/A depending on use site), and except for forestry uses, it is not projected to be applied via typically high inhalation exposure application equipment (e.g., airblast and aerial equipment). However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for indaziflam.

6.2.2 Dermal Postapplication Exposure

All adult and children residential lawn and golf dermal scenarios resulted in MOEs greater than the level of concern (ranging from 2,800 to 90,000) for short-term exposure. A quantitative dermal postapplication assessment was not performed for the Trigger Pump scenario as the amount used is so small that the other scenarios are considered protective of this one use. As

these exposure values were determined using default assumptions (5% of the application rate available as transferable turf residue) it should be noted that exposure would only be lower (greater MOEs) if calculated using actual chemical specific TTR data. Thus use of default assumptions is protective of all postapplication dermal exposure scenarios. Additional details regarding the TTR data are provided in the Indaziflam Occupational and Residential Exposure Assessment (M. Collantes, D372538, April 2010).

Furthermore, since the short- and intermediate-term dermal endpoints are the same, only short-term dermal exposures were assessed for adults and children. HED estimates dermal postapplication exposure based on day-0 residues. Using day-0 residues to assess intermediate-term exposure does not take into account dissipation of residues over time and thus results in a conservative estimation. Therefore, the short-term dermal postapplication exposure assessment represents the worst case scenario and is protective of intermediate-term dermal exposure. A summary of the adult and children short-term dermal exposures is presented in **Table 6.2.2**.

Table 6.2.2: Postapplication Short-term Dermal Exposure and Risk Using Default Assumptions

Scenario	Application Rate (lb ai/A)	TTR [1] ($\mu g/cm^2$)	CF	Short-Term Tc (cm^2/hr)	ET (hrs)	BW (kg)	Dose [2] (mg/kg/day)	MOE [3]
Adults								
Hose-end Sprayer	0.094 (ornamentals & lawn)	0.05264	0.001	14500 - lawn	2	70	0.001592	4,700
	0.047 (lawn)	0.02632					0.000796	9,400
	0.071 *	0.03976					0.0012	6,000
Hand-held Pump Sprayer	0.094 (ornamentals & lawn)	0.05264					0.001592	4,700
Belly Grinder & Granular Push Spreader	0.044	0.02464					0.000745	10,000
	0.071	0.03976					0.0012	6,000
Golfer								
Hose-end Sprayer or Granular Push Spreader	0.071 *	0.03976	0.001	500	4	70	0.0000829	90,000
Children (3 to 6 years)								
Hose-end Sprayer	0.094	0.05264	0.001	5200 - lawn	2	15	0.00266	2,800
	0.047	0.02632					0.0013	5,800
	0.071 *	0.03976					0.0020	3,700
Hand-held Pump Sprayer	0.094	0.05264					0.00266	2,800

Table 6.2.2: Postapplication Short-term Dermal Exposure and Risk Using Default Assumptions.								
Scenario	Application Rate (lb ai/A)	TTR[1] (µg/cm^2)	CF	Short-Term Tc (cm^2/hr)	ET (hrs)	BW (kg)	Dose[2] (mg/kg/day)	MOE[3]
Belly Grinder & Granular Push Spreader	0.044	0.02464					0.001247	6,000
	0.071 *	0.03976					0.0020	3,700

1. Turf Transferable Residues (TTR) = Application Rate x 5% x 11.2
2. Dermal Dose (mg/kg/day) = $\frac{\text{TTR (µg/cm}^2\text{) x 0.001 (mg/µg) x short-term TC (cm}^2\text{/hr) x ET (hr/day) x DAF (7.3\%)}}{\text{BW (kg)}}$
3. Short-term Dermal MOE = NOAEL (7.5 mg/kg/day)/Dermal Dose (mg/kg/day)

* = commercially applied

6.2.3 Oral Exposure

The hand-to-mouth transfer scenario was assessed using the HED Draft Standard Operating Procedures (SOP's) for Residential Exposure Assessments (12/18/97), and the Revisions to the Standard Operating Procedures (SOP's) for Residential Exposure Assessment (Science Advisory Council for Exposure Policy 12, Revised February 22, 2001). This scenario assumes pesticide residues are transferred to the skin of children (ages 3-6 years) during postapplication contact with treated turf areas and are subsequently ingested as a result of hand-to-mouth transfer. Residential postapplication oral exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED.

6.2.3.1 Hand-To-Mouth Exposure and Risk

This scenario assumes that pesticide residues are transferred to the skin of children playing on treated areas and are subsequently ingested as a result of hand-to-mouth transfer. All short- and intermediate-term hand-to-mouth (HTM) scenarios result in MOEs greater than 100 and therefore pose no risk of concern to HED. **Table 6.2.3.1** provides a summary of the short-term HTM exposures.

Table 6.2.3.1: Hand-To-Mouth Exposure and Risk for Children (3 to 6 years)									
Product	TTR[1] (ug/cm^2)	SA (cm^2/event)	FQ	SE	ET (hr/day)	CF1	BW (kg)	Dose[2] (mg/kg/day)	MOE[3]
Short-term									
BCS AA10717 Turf Fertilizer (432-RUOL; 432-RUOA; and 432-RUOT) and 20 WSP (432-RUOO)	3.98E-2	20	20	0.5	2	0.001	15	1.06E-3	7,000
Lawn 3FL (72155-IO)	5.27E-2							1.41E-3	5,300

1. Turf Transferable Residues = (TTR) = AR (0.071 or 0.094 lb ai/A) x F (0.05) x (1-D)^0 x CF2 (4.54E8 µg/lb) x CF3 (2.47E-8 acre /cm^2) = 03.98E-2 or 5.27E-2 ug/cm^2
2. Dose = $\frac{\text{TTR}_t \text{ x SA x FQ x ET x SE x CF1}}{\text{BW}}$
3. MOE = NOAEL (7.5 mg/kg/day)/HTM Dose (mg/kg/day)

6.2.3.2 Object-to-Mouth (Ingestion of Treated Turf) Assumptions and Equations

This scenario estimates doses among young children (3 to 6 years of age) from incidental ingestion of pesticide and/or residential turf grass that has been treated with pesticides. It assumes that pesticide from a treated object or turf is ingested by young children (3 to 6 years of age) who play on treated areas. The object-to-mouth (OTM) scenario results in a MOE greater than 100 and therefore poses no risk of concern to HED. **Table 6.2.3.2** provides a summary of the object-to-mouth exposure and risk.

Table 6.2.3.2: Object-to-Mouth Exposure and Risk for Children (3 to 6 years)

Product	GR[1] ($\mu g/cm^2$)	CF1 (mg/µg)	IgR (cm^2/day)	BW (kg)	Dose[2] (mg/kg/day)	MOE[3]
BCS AA10717 Turf Fertilizer (432-RUOL; 432-RUOA; and 432-RUOT) and 20 WSP (432-RUOO)	1.59E-1	0.001	25	15	2.65E-4	28,000
Lawn 3FL (72155-IO)	2.11E-1	0.001	25	15	3.51E-4	21,000

1. GR (grass residue) = AR x F x $(1\text{-}D)^0$ x CF2 x CF3
2. Dose = GR_0 x IgR x CF1/BW
3. MOE = NOAEL (7.5 mg/kg/day)/Dose (mg/kg/day)

6.2.3.3 Incidental Ingestion of Soil Assumptions, Exposure and Risk

This scenario assumes children who play on treated areas ingest pesticide residues in soil as a result of normal mouthing activities. The soil-ingestion scenario results in a MOE much greater than 100 and therefore poses no risk of concern to HED. This assessment should be considered conservative in that it assumes no dissipation of soil residues would occur over the exposure period. **Table 6.2.3.3** provides a summary of the soil ingestion exposure and risk.

Table 6.2.3.3: Soil Ingestion Exposure and Risk Risk for Children (3 to 6 years)

Product	SR[1] (ug/g)	CF1 (g/µg)	IgR (mg/day)	BW (kg)	Dose[2] (mg/kg/day)	MOE[3]
BCS AA10717 Turf Fertilizer (432-RUOL; 432-RUOA; and 432-RUOT) and 20 WSP (432-RUOO)	5.33E-1	0.000001	100	15	3.56E-6	2.1E6
Lawn 3FL (72155-IO)	7.06E-1	0.000001	100	15	4.71E-6	1.6E6

1. SR_0 (soil residue) = AR(lb ai/A) x F(1) x $(1\text{-}D)^0$ x 0.67 x (4.54×10^8 µg/lb)x (2.47×10^{-8} A/cm^2)
2. Dose (mg/kg/day) = SR_0 (µg/g) x IgR (mg/day) x CF1 (g/µg)/BW (kg)
3. MOE = NOAEL (7.5 mg/kg/day)/ Dose (mg/kg/day)

6.2.3.4 Episodic Ingestion of Granules

This scenario was assessed using the Residential SOP and provides a standard method for estimating postapplication exposure among young children (3 to 6 years of age) from incidental ingestion of pesticide granules. The episodic oral MOE for incidental ingestion of granules is 5,000 and therefore is not of concern to HED. **Table 6.2.3.4** provides a summary or exposure risk.

Table 6.2.3.4: Postapplication Exposure and Risk for Incidental Ingestion of Granules					
Scenario	**IgR (g/day)**	**F**	**CF1 (mg/g)**	**Dose [a] (mg/kg/day)**	**MOE [b]**
Lawn 3FL Granule Reg No 72155-OR	0.3	0.0005	1000	0.001	5,000

a. Dose = IgR x F x CF1 ÷ BW
b. MOE = acute dietary NOAEL (50 mg/kg/day)/Dose

Ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning (thus using the acute dietary endpoint) rather than short -term residue exposure. It should also be noted that the proposed label does indicate that granules should be watered in for proper activation. Watering in granules could further reduce the availability of granules to be potentially ingested.

6.3 Combined Residential Risk Estimates

HED combines risk values resulting from separate exposure scenarios when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population. In evaluating combined residential uses of indaziflam, HED reviewed all non-dietary sources of exposure which consisted of 1.) adult dermal and inhalation handler (lawns only) exposure, 2.) adult and child dermal postapplication exposure and 3.) child postapplication oral exposures. The oral postapplication exposure resulted from hand-to-mouth exposure only, since it represents the worst case of oral exposure. To include exposure from object-to-mouth and soil ingestion in addition to hand-to-mouth could result in a very conservative estimation of exposure as it would overestimate the potential of oral exposure. Similarly, HED does not generally combine adult handler and dermal postapplication exposure as it would result in an over estimate of exposure. **Table 6.3** identifies the combined residential scenarios and MOEs for children simply for use in performing an aggregate exposure assessment in the indaziflam human health risk assessment. There are no risks of concern.

Table 6.3: Combined Residential Exposure and Risk					
Product	**Use Site**	**Handler Total MOE [1]**	**Post-application Dermal MOE [2]**	**Hand-to-Mouth MOE [3]**	**Combined MOE [4]**
Adult					
Lawn 3FL Concentrate /Ready to spray 72155-IO	Lawns, hardscapes and ornamentals	3,000	4,700	NA	NA
Child					
Lawn 3 FL (72155-IO)	Lawns, hardscapes and ornamentals	NA	2,800	5,300	1,800

1. See Table 6.1.2: Indaziflam Residential Handler Exposure and Risk (Hand Held Pump)
2. See Table 6.2.2. Dermal Postapplication Exposure and Risk (DFR data)
3. See Table 6.2.3.1 Hand-To-Mouth Exposure and Risk
4. Adult Combined MOE = NA = HED does not combine adult handler and postapplication exposure
   Child Combined MOE = NOAEL (7.5 mg/kg/day)/dermal postapplication dose (0.00266) + HTM dose (0.00141)

HED did not combine risk resulting from adult homeowner handler, postapplication and golfer exposure to treated turf because HED considers it unlikely that these exposures would co-occur.

7.0 Combined Risk Assessments and Risk Characterization

HED conducted screening level combined risk estimates for short-term exposure durations to ensure that residential and drinking water exposure would not exceed HED's level of concern. In conducting these estimates for indaziflam, HED combined risk values resulting from drinking water and residential scenarios.

To estimate short-term combined risk, HED combined the chronic dietary (water) exposures (as a measure of average dietary exposure) with the short-term residential exposure. HED does not generally combine adult handler and dermal postapplication exposure as it would result in an over estimate of exposure. All short-term combined exposures resulted in MOEs greater than 100 for all populations and are not of concern. Short-term risks are summarized in **Table 7** below.

Table 7: Short-Term Combined Risk Calculations

Population	LOC for Aggregate Risk[1]	MOE drinking water[2]	MOE Total Handler [3]	MOE Dermal Postapplication [4]	MOE Oral [5]	Combined MOE (drinking water + residential) [6]
US Population	100	3700	3,000	4,700	NA	1700
Child (3-6 yrs)	100	2500	NA	2,800	5,300	1100

1 see Table 3.5.9 - basis for the LOC.

2 $MOE_{drinking\ water}$ = See Table 5.2

3 $MOE_{total\ handler}$ = See Table 6.1.2

4. $MOE_{dermal\ postapplication}$ = See Table 6.2.2

5 MOE_{oral} = See Table 6.2.3.1 Hand-To-Mouth Exposure and Risk

6. Adult Combined MOE = (drinking water +total handler) = $\frac{1}{1/MOE_w + 1/MOE_{IH}}$

5 Child Combined MOE = (drinking water + dermal postapplication + oral postapplication) = $\frac{1}{1/MOE_w + 1/MOE_D + /MOE_O}$

8.0 Cumulative Risk Characterization/Assessment

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may, in fact, experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

Several triazine herbicides were determined to have a common mechanism of toxicity based on their ability to disrupt the hypothalamic-pituitary-gonadal axis (US EPA, 2002). The triazine common mechanism group (TCMG) includes atrazine, simazine, propazine, and the metabolites desethyl-s-atrazine (DEA), deisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT). Indaziflam and its metabolite FDAT were considered for incorporation into the TCMG by the HED ToxSAC committee based on structure; indaziflam, FDAT, and the TCMG members contain a common triazine moiety (E. Scollon, D371661, April 21, 2010). However, HED determined that it would not be appropriate to include indaziflam and FDAT in the TCMG for the following reasons: 1) The structures of indaziflam and FDAT are unique in that they contain a fluoroethyl group at the 2-position of the triazine ring; whereas, the TCMG members contain a chlorine substituent at the 2-position of the triazine ring and; 2) Indaziflam and FDAT do not elicit the same toxicological responses shared by the TCMG members. The TCMG members cause an increase in mammary gland tumors in rats and multiple developmental effects such as attenuation of the luteinizing hormone surge, altered pregnancy outcome, and delayed preputial separation. None of these effects were observed in the carcinogenicity or developmental guideline studies for indaziflam. Delayed maturation was observed in the rat reproduction study; however, the effect occurred at the highest dose and was attributed to significant clinical toxicity rather than a perturbation of the hypothalamic-pituitary-gonadal axis. In a non-guideline study, FDAT delayed vaginal potency in a dose dependent manner. However, none of the other characteristic developmental effects of the TCMG members were observed.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for indaziflam or its metabolite FDAT and any other substances, and indaziflam does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of this risk assessment, EPA has not assumed that indaziflam or its metabolite FDAT has a common mechanism of toxicity with other substances.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

(Occupational and Residential Exposure Assessment for Use of the New Active Ingredient Indaziflam on Turf, Golf Courses, Sod Farms, Christmas Tree Farms, Non-Crop Areas and Forestry; M. Collantes: April 2010; D372538)

The proposed use of indaziflam is for control of many annual grasses and broadleaf weeds in turf (lawns, sod farms, golf courses, recreational fields, etc), ornamentals and trees. It is also proposed for use as a pre-emergent herbicide for weed control in parks, railroads, utility, industrial and municipal sites. Indaziflam is available for use by commercial and professional applicators (formulated as a water soluble packet and turf fertilizers). Therefore, the potential for occupational handler and postapplication exposure does exist. Based on the proposed uses, exposures to indaziflam are anticipated to occur for short- and intermediate-term durations.

9.1 Handler Risk

No chemical-specific data were available with which to assess potential exposure for pesticide handlers. The estimates of exposure for pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998) and from the ORETF data. **Table 9.1** presents the estimated risks for workers based on the short- and intermediate-term dermal, inhalation, and total exposures at baseline levels and in few cases the additional use of gloves with the exception of aerial application which included engineering controls. Short- and intermediate-term risks for handlers are not of concern (i.e., MOEs are above 100) and resulted in MOEs ranging from 100 to 840,000. HED used standard assumptions with respect to body weight, areas treated, and use of maximum application rates in assessing occupational exposure. The lowest MOEs were those associated with mixer/loader/applicator (low pressure handwand) for non-crop uses; however, these MOEs are conservative since they did not include the use of gloves which are required on the label.

Table 9.1. Occupational Handler Exposures and Risks										
Exposure Scenario and Product	**Target site**	**Application Rate[a]**	**Area Treated[b]**	**Dermal Unit Exposure[e] (mg/lb)**	**Inhalation Unit Exposure[e] (mg/lb)**	**Dermal Dose[c] (mg/kg/day)**	**Dermal MOE[d]**	**Inhalation Dose[c] (mg/kg/day)**	**Inhalation MOE[d]**	**Total MOE[g]**
Mixer/Loader										
Liquids for Aerial Applications (PHED) *Esplanade F*	forestry	0.125 lb ai/A	1200 A	0.023 single layer/ gloves	0.0012	0.003598	2100	0.002571	2900	1200
Liquids for Ground Applications (PHED) *Esplanade F*	forestry	0.125 lb ai/A	200 A			0.0006	13,000	0.000429	10,000	7,300
Liquids for Ground, and Right-of-Way, Applications (PHED) *Esplanade 200SC*	non-crop areas *	0.089 lb ai/A	25 A	2.9		0.00673	1100	3.81E-5	196,000	1100
Water Soluble Packets Ground Applications (PHED) *BCS-AA10717 20 WSP*	Non-crop areas, turf grass, nurseries, landscapes	0.071 lb ai/A (non-crop)	5 A	0.021	0.00024	7.77E-6	960,000	1.22E-6	6,000,000	830,000
	Golf course and fields grown for ornamentals		40 A			6.22E-5	120,000	9.74E-6	770,000	100,000
	sod farm and , Christmas tree farms		80 A			0.000124	60,000	1.95E-5	390,000	52,000
	forestry	0.088 lb ai/A	200 A			0.000385	19,000	6.0E-5	120,000	17,000
Loading Granules for Tractor Drawn Spreader Applications (PHED) *BCS-AA10717 plus turf fertilizer (0.0142%, 0.0213%, and 0.0284%)*	Lawns, recreational fields and parks	0.071 lb ai/A	5 A	0.0084	0.0017	3.11E-6	2,400,000	8.62E-6	870,000	640,000
	golf course		40 A			2.49E-5	300,000	6.9E-5	100,000	80,000
	sod farm		80 A			4.98E-5	150,000	0.000138	54,000	40,000
Applicators										

Table 9.1. Occupational Handler Exposures and Risks										
Exposure Scenario and Product	**Target site**	**Application Rate[a]**	**Area Treated[b]**	**Dermal Unit Exposure[e] (mg/lb)**	**Inhalation Unit Exposure[e] (mg/lb)**	**Dermal Dose[c] (mg/kg/day)**	**Dermal MOE[d]**	**Inhalation Dose[c] (mg/kg/day)**	**Inhalation MOE[d]**	**Total MOE[g]**
Applying Sprays via Aerial Equipment (PHED)	forestry	0.125 lb ai/A *Esplanade F*	1200 A	0.005 Eng control[f]	0.000068 Eng control[f]	0.00078	9,600	0.000146	51,000	8,100
Applying Sprays via Groundboom Equipment (PHED)	forestry	0.125 lb ai/A *Esplanade F*	200 A	0.014	0.00074	0.000365	21,000	0.000264	28,000	12,000
		0.088 lb ai/A *BCS-AA10717 20 WSP*				0.000257	30,000	0.000186	40,000	17,000
	non-crop areas *	0.089 lb ai/A *Esplanade 200SC*	40 A			0.000052	140,000	3.76E-5	200,000	84,000
	Non-crop sites, turf and recreation fields	0.071 lb ai/A *BCS-AA10717 20 WSP*	5 A			0.00000518	1,400,000	3.75E-6	2,000,000	840,000
	Golf course and field grown for ornamentals and nurseries		40 A			0.0000415	180,000	3.0E-5	250,000	100,000
	Sod and Christmas tree farms,		80 A			0.0000829	90,000	6.0E-5	120,000	52,000
Applying Sprays via Right-of-Way Equipment (PHED)	non-crop areas *	0.089 lb ai/A *Esplanade 200SC*	25 A		0.0039	0.0000325	230,000	0.000124	60,000	48,000
Applying Granules using Solid Broadcast Spreader (PHED)	Lawns, turf, sports and recreation parks	0.071 lb ai/A *BCS-AA10717 plus turf fertilizer (0.0142%, 0.0213%, and 0.0284%)*	5 A	0.0099	0.0063	0.00000367	2,000,000	0.000032	230,000	210,000
	golf courses		40 A			0.0000293	260,000	0.000256	29,000	26,000
	sod farms		80 A			0.0000586	130,000	0.00051	15,000	13,000

Table 9.1. Occupational Handler Exposures and Risks										
Exposure Scenario and Product	**Target site**	**Application Rate**	**Area Treated [b]**	**Dermal Unit Exposure [c] (mg/lb)**	**Inhalation Unit Exposure [c] (mg/lb)**	**Dermal Dose [c] (mg/kg/day)**	**Dermal MOE [d]**	**Inhalation Dose [c] (mg/kg/day)**	**Inhalation MOE [d]**	**Total MOE [g]**
LCO Push Cyclone Granular Spreader (OMA001)ORETF	Lawns, turf, sports and recreation parks	0.071 lb ai/A	5 A	0.35	0.0073	0.00013	56,000	0.000037	200,000	45,000
	golf courses		40 A			0.00104	7,200	0.000296	25,000	5,600
	sod farms		80 A			0.00207	3,600	0.000592	13,000	2,800
Belly Grinder (PHED)	Lawns, turf, sports and recreation parks		1 A	10	0.062	0.00074	10,000	6.29E-5	120,000	9,300
Flaggers										
Flagging for Aerial Sprays Applications (PHED) *Esplanade F*	forestry	0.125 lb ai/A	350 A	0.011	0.00035	0.00050	15,000	0.000219	34,000	10,000
Mixer/Loader/Applicator										
Mixing/Loading/ Applying Liquids with Low Pressure Handwand (PHED)	Forestry *Esplanade F*	0.125 lb ai/A	5 A	100	0.03	0.0652	120	0.000268	28,000	110
		0.0248 lb ai/gal	40 gals	0.43 Single layer & gloves		0.000445	17,000	0.000425	18,000	8,600
	non-crop areas * *Esplanade 200SC*	0.089 lb ai/A	5 A	100		0.0464	160	0.000191	39,000	160
		0.0178 lb ai/gal	40 gals			0.07425	100	0.000305	25,000	100
Mixing/Loading/ Applying Liquids with Back Pack (PHED)	Forestry *Esplanade F*	0.125 lb ai/A	5 A	2.5		0.00163	4600	0.000268	28,000	4,000
		0.0248 lb ai/gal	40 gals			0.00258	3,000	0.000425	18,000	2,500
	non-crop	0.089 lb ai/A	5 A			0.00116	6,500	0.000191	39,000	5,600

Table 9.1. Occupational Handler Exposures and Risks										
Exposure Scenario and Product	**Target site**	**Application Rate[a]**	**Area Treated [b]**	**Dermal Unit Exposure [e] (mg/lb)**	**Inhalation Unit Exposure [e] (mg/lb)**	**Dermal Dose [c] (mg/kg/day)**	**Dermal MOE [d]**	**Inhalation Dose [c] (mg/kg/day)**	**Inhalation MOE [d]**	**Total MOE [g]**
	areas* *Esplanade 200SC*	0.0178 lb ai/gal	40 gals			0.00185	4,000	0.000305	25,000	3,500
Mixing/Loading/ Applying Liquid Concentrates with a Handgun Sprayer (LCO ORETF)	Non-crop sites, turf, recreation fields, Christmas tree farms, ornamentals and nurseries	0.071 *BCS-A10717 20 WSP*	5 A	0.64	0.0072	0.000237	32,000	0.0000365	200,000	27,000
		0.089 *Esplanade 200SC*		0.45	0.0018	0.000209	36,000	1.14E-5	650,000	34,000

a Application rates = maximum application rates from labels.
b Amount handled per day values are HED estimates of acres treated or gallons applied per day based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.
c Dose (mg/kg/day) = Unit exposure(mg/lb ai) x App Rate (lb ai/acre) x Area Treated (acres/day) x %Absorption (7.3% dermal and 100% inhalation) / Body weight (70 kg).
d MOE = NOAEL (7.5 mg/kg/day) / Dose (mg/kg/day)
e All scenarios were run at Baseline (dermal - single layer clothing; Inhalation - no respirator) unless otherwise specified.
f. Eng Con: Engineering control is enclosed cab, or enclosed cockpit.
g. Total MOE = NOAEL (7.5 mg/kg/day) / Dermal Dose + Inhalation Dose (mg/kg/day)
*non crop areas = rail road yards, roadsides, ornamental and perennial plantings, fence rows, utilities, hardscapes, industrial, municipal and government sites.

9.2 Occupational/Commercial Postapplication Exposure

9.2.1 Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative postapplication inhalation exposure assessment was not performed for indaziflam at this time primarily because it has a very low vapor pressure (vapor pressure 5 x 10^{-10} mmHg at 25°C), it is applied at low application rates (maximum rates range from 0.089 - 0.125 lbs ai/A depending on use site), and except for forestry uses, it is not projected to be applied via typically high inhalation exposure application equipment (e.g., airblast and aerial equipment). However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for indaziflam.

9.2.2 Postapplication Dermal Exposure

Exposures during postapplication activities were estimated using dermal transfer coefficients from the Science Advisory Council for Exposure Policy Number 3.1: Agricultural Transfer Coefficients, August 2000, and default assumptions (5% of application rate available as transferable residue for turf and 20% for ornamentals). Since the short- and intermediate-term dermal endpoints are the same, only short-term dermal exposures were assessed for workers. HED estimates dermal postapplication exposure based on day-0 residues. Using day-0 residues to assess intermediate-term exposure does not take into account dissipation of residues over time and thus results in a conservative estimation. Therefore, the short-term dermal postapplication exposure assessment represents the worst case scenario and is protective of intermediate-term dermal exposure. All short-term postapplication dermal exposures resulted in MOEs greater than 100 (ranging from 1,400 to 45,000) and therefore were not of concern. **Table 9.2.2** provides a summary of the postapplication exposures and risk for indaziflam.

Table 9.2.2: Postapplication Exposure and Risks for Indaziflam Using Default Assumptions

Scenario	Tc [1] (cm^2/hr)	DAT [2]	DFR or TTR [3] (ug/cm^2)	DOSE [4] (mg/kg/day)	MOE [5]
Sod farm & Golf Course Mowing	500	0	0.0398 [a]	0.000166	45,000
Hand weeding & transplant of turf	16,500	0		0.00547	1,400

Table 5.2.2. Postapplication Exposure and Risk for Indaziflam Using Default Assumptions					
Scenario	Tc [1] (cm^2/hr)	DAT [2]	DFR or TTR [3] (ug/cm^2)	DOSE [4] (mg/kg/day)	MOE [5]
Outdoor ornamentals	110	0	0.199 [b]	0.000183	41,000
Moving ornamentals in pots to trucks and reorganizing	400	0		0.00066	11,000
Christmas Trees thinning	3000	0	0.159 [c]	0.0040	1900

1. Tc = transfer coefficient (cm^2/hr)
2. DAT = Days after treatment

3.a TTR = application rate (0.071 lb ai/A) x (1- daily dissipation rate)^t x 4.54E8 ug/lb x 24.7E-9 A/cm^2 x 5 % application rate available for transfer from turf

3b DFR = application rate (0.089 lb ai/A) x (1- daily dissipation rate)^t x 4.54E8 ug/lb x 24.7E-9 A/cm^2 x 20% fraction of residues retained on foliage (ornamentals) after initial treatment.

3c. DFR = application rate (0.071 lb ai/A) x (1- daily dissipation rate)^t x 4.54E8 ug/lb x 24.7E-9 A/cm^2 x 20% fraction of residues retained on foliage (Christmas trees) after initial treatment.

4. Dermal Dose = [TTR (ug/cm^2) x Tc (cm^2/hr) x 0.001 mg/ug x 8 hrs/day x 7.3%DA] ÷ body weight (70 kg)
5. MOE = NOAEL (7.5 mg/kg/day)/Dermal Dose

Restricted Entry Interval

The restricted entry interval (REI) listed on proposed labels is based on the acute toxicity of the technical material. Indaziflam has low acute dermal toxicity (Toxicity Category III) and is not an ocular or dermal irritant or a dermal sensitizer (Category IV). Acute toxicity Category III and IV chemicals require a 12- hour REI. Furthermore, all short -term postapplication dermal exposures resulted in MOEs greater than the level of concern (MOE>100) and therefore were not of concern. Therefore the 12-hour REI which appears on the proposed labels is adequate and not of concern to HED.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

Based on the available toxicity database and the Agency's current practices, the inhalation risk for indaziflam was assessed using an oral toxicity study. The Agency sought expert advice and input on issues related to this route to route extrapolation approach (i.e. the use of oral toxicity studies for inhalation risk assessment) from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route to route extrapolation of toxicity data. If any new policies or procedures are developed, the

Agency may revisit the need for an inhalation toxicity study for indaziflam and/or a re-examination of the inhalation toxicity risk assessment.

10.2 Residue Chemistry

None

10.3 Occupational and Residential Exposure

None

References:

1. Indaziflam: Occupational/Residential Exposure Assessment for Use of Indaziflam on on Turf, Golf Courses, Sod Farms, Christmas Tree Farms, Non-Crop Areas and Forestry (M. Collantes, D372538; April 2010)

2. Tier 2 Drinking Water Assessment for the Section 3 New Chemical Registration of Indaziflam; Rueben Baris; D356141; and D367447; February 2, 2010.

Appendix A: Toxicology Assessment

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for turf and food use for indaziflam are shown below in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical Indaziflam	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes[1]
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	--
870.6100b	90-Day Neurotoxicity (hen)	no	--
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	--
	Subchronic Oral (rat)	no	--
	Six-month Oral (dog)	no	--

1 Satisfied by 870.4300.

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Indaziflam technical

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - rat	47443281	LD_{50} > 2000 mg/kg (both sexes)	III
870.1200	Acute dermal - rabbit	47443282	LD_{50} > 2000 mg/kg (both sexes)	III
870.1300	Acute inhalation - rat	47443283	LC_{50} > 2.3 mg/L (both sexes)	IV
870.2400	Acute eye irritation - rabbit	47443284	Non-irritant	IV
870.2500	Acute dermal irritation - rabbit	47443285	Non-irritant	IV
870.2600	Skin sensitization - guinea pig	47443286	Not a sensitizer (Buehler method)	N/A

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	47443287 (2005) Acceptable/Guideline 0, 200, 5000 or 10,000 ppm in diet for 13 weeks M: 0, 14, 338 or 689 mg/kg/day F: 0, 16, 410 or 806 mg/kg/day 98.7% a.i.	NOAEL = 14/410 mg/kg/day M/F LOAEL = 338/806 mg/kg/day M/F, based on: in males at 338 mg/kg/day, increased TSH at Week 3 and diffuse thyroid follicular cell hypertrophy at Week 13; in females at 806 mg/kg/day, mortality (one female, sacrificed *in extremis* with clinical signs, decreased motor activity and gastric red foci), marginally decreased body weights and decreased food consumption.
870.3100	90-Day oral toxicity (mouse)	47443288 (2005) Acceptable/Guideline 0, 100, 500 or 1200 ppm in diet for 13 weeks M: 0, 19, 91 or 218 mg/kg/day; F: 0, 23, 118 or 256 mg/kg/day 96.5% a.i.	NOAEL = 91/118 mg/kg/day M/F LOAEL = 218/256 mg/kg/day M/F, based on increased mortality and wasted appearance (females), hunched posture in males and females, decreased body weight/weight gain and food consumption in males and females.
870.3150	90-Day oral toxicity (dog)	47443289 (2008) Acceptable/Guideline 0, 7.5, 15 or 30 mg/kg/day by gavage 94.5-99.4% a.i.	NOAEL = 7.5 mg/kg/day M/F LOAEL = 15 mg/kg/day, based on axonal degeneration in the brain, spinal cord and sciatic nerve in males and females. At 30 mg/kg/day, 3 animals were sacrificed with seizures by Day 30; all remaining group animals were sacrificed on Day 36. Decreased body weight gain and neuropathology were observed.
870.3200	28-Day dermal toxicity (rat)	47443290 (2006) Acceptable/Guideline 0, 40, 200 or 1000 mg/kg/day applied to skin 5 days/week for 4 weeks (22/23 total applications in M/F) 90.32% a.i.	**Systemic** NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day) **Local dermal** NOAEL = 1000 mg/kg/day LOAEL = not determined (>1000 mg/kg/day). Some indication of local dermal irritation was observed at all doses but the findings were transient and observed only in females, and therefore were not considered adverse.
870.3700a	Prenatal developmental in (rat)	47443291 (2006) Acceptable/Guideline 0, 10, 25 or 200 mg/kg/day by gavage in 0.5% aqueous methylcellulose, GD 6 through 20	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on decreased fetal body weights.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		94.5% a.i.	
870.3700b	Prenatal developmental in (rabbit)	47443292 (2008) Acceptable/Guideline 0, 10, 25 or 60 mg/kg/day by gavage in 0.5% aqueous methylcellulose, GD 6 through 28 93.14% a.i.	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 60 mg/kg/day based on decreased maternal body weight gain and food consumption and macroscopic changes in the liver in one doe. **Developmental** NOAEL = 60 mg/kg/day LOAEL = not established (>60 mg/kg/day).
870.3800	Reproduction and fertility effects (rat)	47443293 (2008) Acceptable/Guideline 0, 150, 1000 or 8000 ppm in the diet; F1 high dose reduced to 4000 ppm at 5-17 days' postweaning Average P/F_1 consumption (note: high dose not averaged due to F1 dose reduction) M: 0, 10.4, 69.3 or 560.1 mg/kg/day (P males) and 317.6 mg/kg/day (F_1 males, due to reduction in dietary dose) F: 0, 12.9, 85.2 or 656.2 mg/kg/day (P females) and 355.2 mg/kg/day (F_1 females, due to reduction in dietary dose) 93.14-94.5% a.i.	**Parental** NOAEL = 69.3/85.2 mg/kg/day M/F LOAEL = 560.1/656.2 mg/kg/day M/F, based on coarse tremors in females from Weeks 6-17 and in gestation and lactation, decreased body weight/weight gain and food consumption and renal toxicity (tubular degeneration/ regeneration and increased weight) in males. **Offspring** NOAEL = 69.3/85.2 mg/kg/day M/F LOAEL = 317.6/355.2 mg/kg/day M/F, based on clinical signs (perianal, urine or nasal staining, diarrhea or soft stool, distended abdomen, weakness, tremors, myoclonus, increased activity and reactivity) and decreased pup body weights throughout postnatal period. **Reproductive** NOAEL = 69.3/85.2 mg/kg/day M/F (based on F1 intakes) LOAEL = 317.6/355.2 mg/kg/day M/F, based on delayed sexual maturation in males and females (% pups reaching criterion unaffected).
870.4100a	Chronic toxicity (rat)	47443296 (2007) Acceptable/Guideline 0, 300, 3000 or 10,000 ppm in the diet (6000 in females after Day 280) equivalent to average daily intake of M: 0, 14, 136 or 474 mg/kg/day; F: 0, 19, 185 or 589 mg/kg/day 93.14% a.i.	NOAEL = 19 mg/kg/day F, 136 mg/kg/day M; LOAEL = 185 mg/kg/day F, based on increased mortality, clinical signs of toxicity, mydriasis and absence of papillary reflex; 474 mg/kg/day M, based on decreased body weight/weight gain and food consumption.
870.4100b	Chronic toxicity (dog)	47443294 (2008; main study);47443295 (2007; dietary stability)	NOAEL = 2.0 mg/kg/day LOAEL = 6/7 mg/kg/day M/F, based on axonal degeneration of nerve fibers in the brain, spinal cord and sciatic nerve in males and females.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		Acceptable/Guideline 0, 60, 225 or 450 ppm in the diet M: 0, 2, 6 or 12 mg/kg/day; F: 0, 2, 7 or 11 mg/kg/day 93.16% a.i.	Marginal body weight decreases early in study seen at 12/11 mg/kg/day M/F.
870.4200a	Carcinogenicity (rat)	See 870.4300, below	
870.4200b	Carcinogenicity (mouse)	47743416 (2008) Acceptable/Guideline 0, 50, 250 or 1000 ppm in diet M: 0, 6.8, 34 or 142 mg/kg/day; F: 0, 8.4, 42 or 168 mg/kg/day 93.14% a.i.	NOAEL = 34/42 mg/kg/day M/F LOAEL = 142/168 mg/kg/day M/F, based on decreased body weight/weight gain and food consumption, M/F; renal and hepatotoxicity in males; stomach and ovarian toxicity in females. **No evidence of carcinogenicity**
870.4300	Combined carcinogenicity/ chronic toxicity (rat)	47743417 (2009) Acceptable/Guideline 0, 300, 3000 or 10,000 ppm in the diet M: 0, 12, 118 or 414 mg/kg/day; F: 0, 17, 167 or 452 mg/kg/day 93.14% a.i.	NOAEL = 12/17 mg/kg/day M/F LOAEL = 118/167 mg/kg/day M/F, based on decreased body weight/weight gain, signs of neurotoxicity (various symptoms, including dilated pupils, tremors, limb/movement effects, reduced activity/alertness) and renal toxicity in females, liver toxicity in males and females and atrophic seminal vesicles and increased TSH (Week 3 only) and thyroid colloid alteration in males. Thyroid alterations in males appeared to be secondary to liver effects. Decreased survival was observed at 452 mg/kg/day in females and both males and females showed more pronounced clinical signs of toxicity. **No evidence of carcinogenicity**
Gene Mutation 870.5100	Bacterial reverse gene mutation assay (*S. typhimurium*)	47443297 (2006) Acceptable/Guideline 0, 16, 50, 158, 500, 1581 or 5000 µg/plate in presence or absence of S9 activation. Trial 1 – plate incorporation method and Trial 2, pre-incubation method 90.32% a.i.	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA 102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (500 µg/plate) and precipitating concentrations (5000 µg/plate).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100	Bacterial reverse gene mutation assay (*S. typhimurium*)	47443301 (2007) Acceptable/Guideline Trial 1: 0, 15, 50, 158, 500, 1502 or 5000 µg/plate in the presence or absence of S9 activation, plate-incorporation method Trial 2: 0, 100, 200, 400, 800, 1600 or 3200 µg/plate in the presence or absence of S9 activation, pre-incubation method 95.7% a.i.	**Negative** +/-S9 activation in *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 for increased frequency of revertant colonies up to cytotoxic (≥800 µg/plate) and precipitating (3200 µg/plate) concentrations.
Gene Mutation 870.5300	Mammalian cell *in vitro* forward gene mutation (cultured V79 cells, HGPRT locus)	47443302 (2006) Acceptable/Guideline 0, 10, 100 or 1000 µg/mL in presence or absence of S9 activation 90.32% a.i.	**Negative** for increased frequency of mutation in CHO cells (not cytotoxic).
Cytogenetics 870.5375	Mammalian *in vitro* cytogenetic assay (Chinese hamster V79 lung cells)	47443305 (2006) Acceptable/Guideline 4 hr exposure, 14 hr recovery period: 0, 15, 30, 60, 90 or 120 µg/mL in the absence of S9 activation; 0, 50, 100, 160, 200 and 240 µg/mL in the presence of S9 activation. 4 hr exposure, 26 hr recovery period: 0, 60, 90 and 120 in the absence of S9 activation; 0, 160, 200 and 240 µg/mL 18 hr exposure, no recovery period in the absence of S9 activation: 0, 4, 8, 16, 20 and 24 µg/mL 90.32% a.i.	**Negative** for induction of chromosomal aberrations above background in the presence or absence of S9 metabolic activation. Tested up to the limit of solubility (160 µg/mL, -S9)
Cytogenetics 870.5395	Mammalian *in vivo* micronucleus assay (mouse)	47443308 (2006) Acceptable/Guideline Two doses of 0, 10, 20 or	**Negative** for induction of increased frequency of micronucleated polychromatic erythrocytes in bone marrow at any treatment time.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		40 mg/kg by IP injection in 0.5% aqueous Cremaphor vehicle administered 24 hrs apart; harvested 24 hrs after second dose 90.32% a.i.	
870.6200a	Acute neurotoxicity screening battery (rat)	47443310 (2008) Acceptable/Guideline 0, 50, 100 or 2000 mg/kg by gavage in corn oil. Time of peak effect estimated at 50 min postdosing. 93.14% a.i.	NOAEL = 50 mg/kg LOAEL = 100 mg/kg based on decreased motor and locomotor activity in females (threshold effect level). Lower NOAEL/LOAEL relative to subchronic study likely due to gavage vs. dietary administration.
870.6200b	Subchronic neurotoxicity screening battery (rat)	47443309 (2008) Acceptable/Guideline 0, 200, 4000 or 8000/10,000 ppm (M/F) equivalent to average daily intake in the diet of M: 0, 12.2, 243.6 or 585.7 mg/kg/day F: 0, 15.1, 306.9 or 580.9 mg/kg/day 93.14% a.i.	NOAEL = 243.6/306.9 mg/kg/day M/F LOAEL = 585.7/580.9 mg/kg/day M/F, based on decreased total session motor and locomotor activity in females, clinical signs/FOB effects in males and females (tremors, repetitive chewing motion and perianal and lacrimal staining), decreased body weights (females) and cumulative body weight gain in males and females.
870.6300	Developmental neurotoxicity (rat)	47443311 (2008) Acceptable/Nonguideline 0, 150, 1000 or 7000 ppm in the diet (high dose reduced to 4000 ppm on LD4) equivalent to average daily intake in the diet of 0, 13, 83.8 or 432 mg/kg/day 93.14% a.i.	**Maternal** NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day, based on clinical signs at daily observation and FOB assessment (coarse tremors, dilated pupils and dilated pupils unresponsive to penlight, nasal staining, repetitive chewing movements), decreased body weights/weight gain and reduced number of litters (-17%). **Offspring** NOAEL = 83.8 mg/kg/day LOAEL = 432 mg/kg/day, based on decreased body weight through PND 21 in males and females. Males postweaning had slightly decreased body weights. Decreased motor activity (-29%) on PND 21 in males was considered treatment-related, but was not seen at other measurement times nor in females.
870.7485	Metabolism and pharmacokinetics	47443312 (2008) Acceptable/Guideline	Absorption was complete (>90% bioavailability) and rapid, with radioactivity

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	(rat) – tier 1	Male rats given single gavage dose of either ^{14}C-indane labeled or -triazine labeled indaziflam at 11.5-14.98 mg/kg. Mass balance groups – excreta collected for 3 days postdosing. Bile-duct cannulated groups – bile and excreta collected for 2 days postdosing. 99-100% radiochemical purity	found in bile by 1 hr postdosing and most radioactivity (generally around 90%) excreted by 24 hrs. Tissue levels of radioactivity were low (0.2% of administered dose by 3 days) with highest levels observed in the GIT, liver, kidney, skin and thyroid. In the bile duct-cannulated animals, tissue levels were about 2-4 times greater in the triazine-labeled group than the indane-labeled group but levels in other groups were similar. Excretion was largely fecal (62-70%), with significant biliary excretion observed. CO_2 exhalation was negligible. Parent compound was identified at between 2-16% of dose in urine and feces. Major routes of metabolism were oxidative pathways; glucuronide conjugation also observed. Major metabolite was carboxylic acid, found in urine, bile and feces. Numerous other metabolites identified or characterized; profile varied among dose groups. Other metabolites identified at low levels included the 3-hydroxyindane acid epimer, diaminotriazine and 3-ketohydroxymethyl metabolites.
870.7485	Metabolism and pharmacokinetics (rat) – tier 2	47743418 (2009) Acceptable/Guideline Single gavage doses as follows: (1) low dose mass balance studies in females given ^{14}C-indane-labelled indaziflam at 4.8 mg/kg or ^{14}-triazine-labelled indaziflam at 8.8 mg/kg; (2) high dose mass balance studies in males given ^{14}C-indane-labelled indaziflam at 559 mg/kg or ^{14}-triazine-labelled indaziflam at 723 mg/kg; (3) plasma pharmacokinetic experiments with indane-label at 2.9 mg/kg (females) or 13.7 mg/kg (males) or triazine-label at 13.2 mg/kg (females) or 16.3 mg/kg (males). Radiochemical purity 99%	Absorption was rapid (radioactivity detected in blood by 5 minutes and peak blood concentrations observed between 40-60-minutes postdosing; rapidly decreasing thereafter) Females showed slightly higher absorption than males. Excretion was rapid (>87% by 24 hrs) and was equally distributed between urine and feces in females but was greater in feces in males (10:1). CO_2 excretion was negligible. Radioactivity was not retained at significant levels in tissues; the GIT, liver and skin showed the highest residues. The carboxylic acid metabolite was the major metabolite in both high dose males and low dose females, which was found in urine and feces. Additional metabolites present at >5% of dose included 3-hydroxyindane acid metabolite in low dose females, dihydroxy metabolite in low dose females and hydroxyethyl acid metabolite in the high dose males (indane-label).
870.7600	Dermal	47743420 (2008)	Absorption was inversely proportional to dose,

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile – Indaziflam technical			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	absorption, *in vivo* (rat)	Acceptable/Guideline 0.5, 2 or 5000 µg ai/ cm^2 on 12 cm^2 skin for 8 hrs to male rats; absorption evaluated after 8, 24, 72 and 168 hr postdosing Radiochemical purity >98%	indicating saturation of skin penetration with increasing dose. Between 0.4-20.4% of the applied dose was recovered in combined residual carcass, excreta, blood and non-treated skin. Based on decreased radioactivity at the application site, the most conservative value for risk assessment is a dermal absorption of 42.7% observed at 0.5 µg ai/ cm^2 at 8 hr postapplication.
870.7800	Immunotoxicity - rat	47443313 (2008) Acceptable/Guideline 0, 300, 3000 or 6000 (females) or 10,000/6000 (males) ppm in the diet equivalent to average daily intake in the diet of M: 0, 27.7, 258 or 528 mg/kg/day F; 0, 31, 334.2 or 737.9 mg/kg/day 93.12% a.i.	**Systemic** NOAEL = 258.8/334.2 mg/kg/day M/F LOAEL = 528/737.9 mg/kg/day M/F, based on mortality (one male sacrificed *in extremis)*, clinical signs of toxicity in males and females (including tremor, abnormal gait, pallor, hunched back), decreased food and water consumption in males and decreased body weight/weight gain in males and females. **Immunotoxicity** NOAEL = 528/737.9 mg/kg/day M/F LOAEL = not established (>528/737.9 mg/kg/day M/F)
Non-guideline	*In vitro* dermal absorption – rat and human skin	47743419 (2007) Acceptable/Nonguideline Application of a 10µL/ volume of concentrated 500 mg/mL formulation and representative spray dilutions of 0.5, 0.2 or 1.0 mg/mL to excised human and rat dermatomed skin. Exposure duration was 24 hr. Radiochemical purity >98%	Total absorbed dose decreased with increasing concentration, indicating saturation of skin penetration with increasing dose. Rat skin was 3.8 to 10.7 times more permeable than human skin over 24 hr at the concentrations tested.

Toxicity Profile - FDAT			
Nonguideline Study	Sexual maturation supplemental study (rat)	47443314 (2008) Acceptable/Nonguideline 0, 18.0, 36.5, 72.9 or 145.8 mg/kg/day by gavage to LD21 offspring and timed-pregnant female Wistar rats: administered daily until PND 41	NOAEL = 36.5 mg/kg/day LOAEL = 72.9 mg/kg/day, based on delays in vaginal patency (+2.3 days, increasing to 3.9 days at 145.8 mg/kg/day). Also at high dose, body weight was decreased and salivation and urine staining were observed.

Appendix B. Input Values for the Drinking Water Exposure Assessment

U.S. Environmental Protection Agency Ver. 2.02

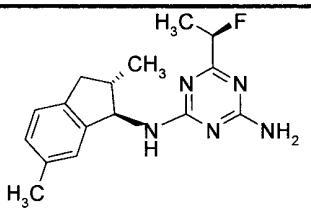
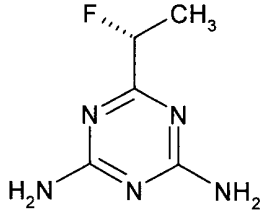
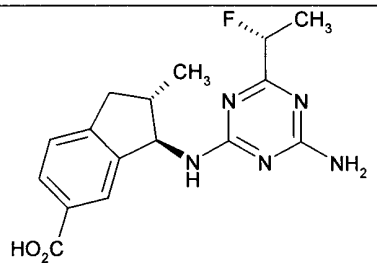
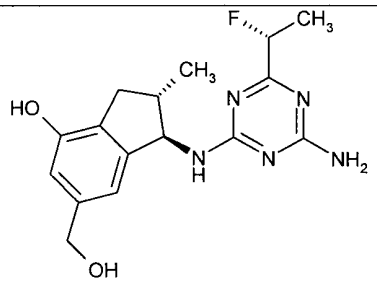
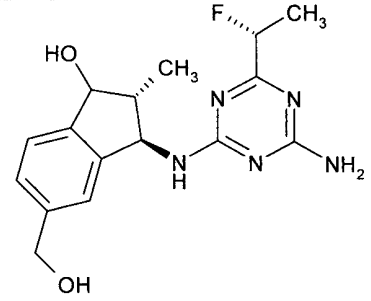
DEEM-FCID Acute analysis for INDAZIFLAM
Residue file name: C:\Documents and Settings\mdoherty\My Documents\Chemistry Reviews\DEEM Runs\Indaziflam\Indaziflam Water Acute.R98
Analysis Date 04-20-2010 Residue file dated: 04-20-2010/10:28:23/8
Reference dose: aRfD = 0.5 mg/kg bw/day NOEL = 50 mg/kg bw/day

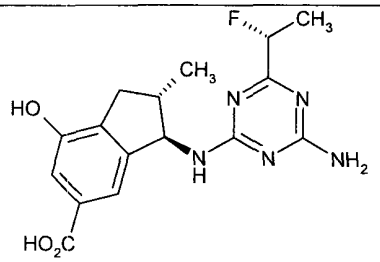
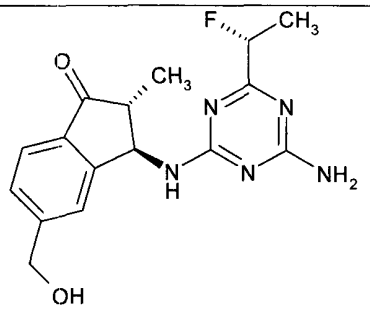
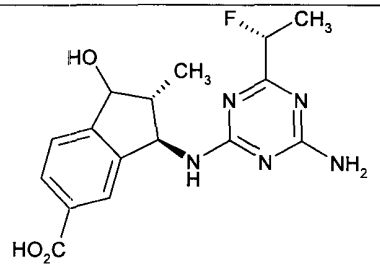
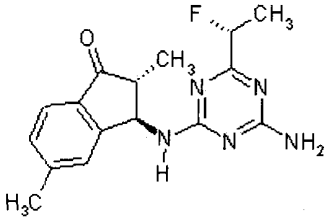
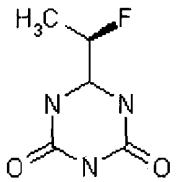
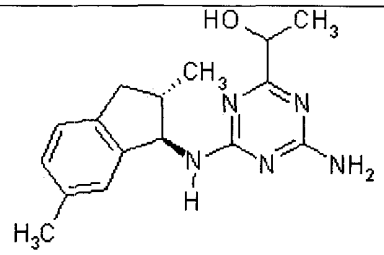
EPA Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
86010000	O	Water, direct, all sources	0.084000	1.000	1.000	
86020000	O	Water, indirect, all sources	0.084000	1.000	1.000	

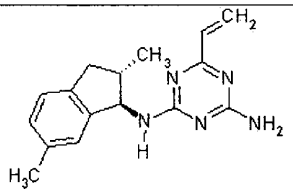
Filename: C:\Documents and Settings\mdoherty\My Documents\Chemistry Reviews\!DEEM Runs\Indaziflam\Indaziflam Water Chronic.R98
Chemical: Indaziflam
RfD(Chronic): .02 mg/kg bw/day NOEL(Chronic): 2 mg/kg bw/day
RfD(Acute): .5 mg/kg bw/day NOEL(Acute): 50 mg/kg bw/day
Date created/last modified: 04-20-2010/10:29:16/8 Program ver. 2.03

EPA Code	Crop Grp	Commodity Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
86010000	O	Water, direct, all sources	0.026000	1.000	1.000	
86020000	O	Water, indirect, all sources	0.026000	1.000	1.000	

APPENDIX C: Table of Structures

Table 1: Major Chemicals Identified in Metabolism and Fate Studies		
Compound/Code	Chemical Name	Chemical Structure
Indaziflam	1,3,5-triazine-2,4-diamine, N-[(1R,2S)-2,3-dihydro-2,6-dimethyl-1H-inden-1-yl]-6-[(1R)-1-fluoroethyl]-	
Fluoroethyl diaminotriazine (FDAT)	6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine	
Indaziflam carboxylic acid	(2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-2,3-dihydro-2-methyl-1*H*-indene-5-carboxylic acid	
Indaziflam-4-hydroxyhydroxymethyl	(2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-5-hydroxymethyl-2,3-dihydro-2-methyl-1*H*-indene-7-ol	
Indaziflam-dihydroxy	(2*R*,3*R*)-3-({4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl}amino)-5-hydroxymethyl-2-methylindan-1-ol	

Indaziflam-4-hydroxy acid	(2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-2,3-dihydro-2-methyl-1*H*-indene-7-ol-5-carboxylic acid	
Indaziflam-3-ketohydroxymethyl	(2*S*,3*R*)-3-[[4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl]amino)-5-hydroxymethyl-2-methylindane-1-one	
Indaxiflam-3-hydroxyindane	(2*R*,3*R*)-3-({4-amino-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazin-2-yl}amino)-2-methylindan-1-ol-5-carboxylic acid	
Indaziflam ketone (triazine indanone)	N-[(1R,2S)-2,3-Dihydro-2,6-dimethyl-3-oxo-1H-inden-1-yl]-6-[(1R)-1-fluoroethyl]-1,3,5-triazine-2,4-diamine	
Fluoroethyltriazinane-2,4-dione (dihydroamino triazine; ROI1)	6-[(1R)-1-fluoroethyl]-1,3,5-triazinane-2,4-dione	
Indaziflam hydroxyethyl	1-{4-Amino-6-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1H-inden-1-ylamino]-1,3,5-triazin-2-yl}ethanol	

Indaziflam olefin	N-[(1R,2S)-2,6-dimethyl-2,3-dihydro-1H-inden-1-yl]-6-vinyl-1,3,5-triazine-2,4-diamine	

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